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Toxicological Analysis of Bisphenol -A with the Help Of Softwares And Docking Tools

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ABSTRACT

Bisphenol A, a major constituent of the plastic, is creating an utter menace for this Anthropological and Biological world and is challenging our genesis in various ways.After the plastic revolution started with the accidental introduction of Bakelite, plastic has been chocking this planet and is threatening our own survival. Obstructing airways of birds and mammals, poisoning the groundwater, inflicting a threatening blow to the soil ecosystem, clogging the water holes are some of the major threats posed by plastic. In this paper, we are discussing about the potential threat caused by Bisphenol A, the cardinal facet of plastic, through various toxicological studies and molecular docking analysis.

Keywords: Bisphenol-A, Molecular Receptor, Toxicity Analysis, Molecular Docking, Mutagenicity.

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1. INTRODUCTION

The world was first petrified in the year 1909, when Leo Baekeland, a chemist from Belgium working in America, founded Bakelite.[1] Reasons for the reaction was quite simple, the material was found to be fire resistant, extremely malleable, and can be produced in a mass with accurately high productivity.[1][2]This features were found to be extremely economic and replaced those used in those times and soon converted into its successor, the modern day plastic, with a melange of silhouettes. [1]Soon after a few decades, the world started to understand the true complexion of plastic, and this shock turned out to be a catastrophe cause scientists and sea farers started to discover, in their utter horror, the murderous trail of plastic (Fig 1);[3] dead birds and fishes struck in plastic nets, bags and even some of them have entered the airways, preventing the poor species to suffer an unimaginable death.[4] However, for the industries and multinational corporate, production gained a new height with the introduction of globalization in the third world countries and the silicon revolution. [5]The trend continued for another couple of decades until coming to a plateau, and now it is experiencing a slow decline as more and more eco friendly reusable materials are coming into the market and as the world is becoming more aware of the destructive behaviour this tiny little piece of organic polymer has caused.[5][6][7]

In these days, wads of industries are still manufacturing plastics for the third world countries, the ones who can't manage their own economic plight and so abstained themselves from using the eco-friendly materials at an exorbitant capital.[8][9] Hosting nearly 75% of the world's population, the third world dominions poses as a threat on the development and mass production of eco-friendly products.[8] Corporates of the first world countries should also be prevented from continuing this horrific trade. Derelict economic conditions, abysmal management of the authorities have put the future of plastic usage in those areas uncertain.[9][10]

In the worldwide scenario, governments are still at dilemma whether to accept the eco friendly products or to revise their economic reforms.[11] Incidents like felonious dumping of waste in foreign territorial water have gained major attention in the United Nations, and conventions and treaties were signed to enforce the perpetrators and made them abide the rules.[12] [13][14] But little could be done of that one cause loopholes in those acts have made malefactors escape justice and degrade the marine ecosystems. Several genres of plastics are there with a diverse range of utilization of which a few of them should be termed as "chokers" because of their resilience to environmental degradation and also because their abhorrent behaviour which they expose while chocking drains and airways of living species.[15]Of them all the Polyvinyl Chloride (PVC) are the worst causative agents of these malicious works.[16] Bisphenol-A is just a constituent of it providing and supporting it the details of its works. [17]

Bisphenol-A got is possessed with a mass of 240.3811 amu along with a logP of 3.1148. A couple of H bond acceptors donors and rotatable bonds are present along with a PSA of 40.4600. There is no RO5 violations but a single Ro3 violation is detected.[18]

Bisphenol-A, trailblazer of the plastic clan , is a compound allied with the diphenylmethane family .Its constituent with the plastic deals in a major way since it forms the backbone and got tremendous hold of the properties of the plastics .[19]Toxicological studies have longed been interested in the toxicity of Bisphenol - A . (Borrell et. al. ,2010) studied on the role of Bisphenol-A, acting as a catalyst to induce prostate cancer.

In her horror, it is seen that the product not only causes prostate cancer but also a wide number of ailments, of which some are cancerous. [20] Another work by (Poole et. al. , 2007) founded that Bisphenol-A diglycidylether , another derivative is causing no reproductive and developmental toxicity. [21] In1999, (Cagen et. al.) found out that Bisphenol A at a low dose cant induce terratogenic or reproductive toxic effect at CF1 mice.[22] In 2003, (Bindhumol et. al,) found that Bisphenol-A can produce reactive oxygen species in the liver of male rat.[23] In 2000 , (Pottenger et. al.) studied bioavailability of Bisphenol-A found that the bioavailability of Bisphenol-A is a slight lower through oral administration than through intraperitonial or subcutaneous administration .[24] (Saal et. al., 1998) found out that Bisphenol-A can significantly curtail sperm production and epididymeds size but can also exacerbate preputial glands.[25]

Bisphenol-A can intrude into the ecosystem through various routes either individually or through a rendezvous with other compounds and elevating its toxicity through synergistic ways. It can also infiltrate the groundwater through the pores and can eventually spike the groundwater.

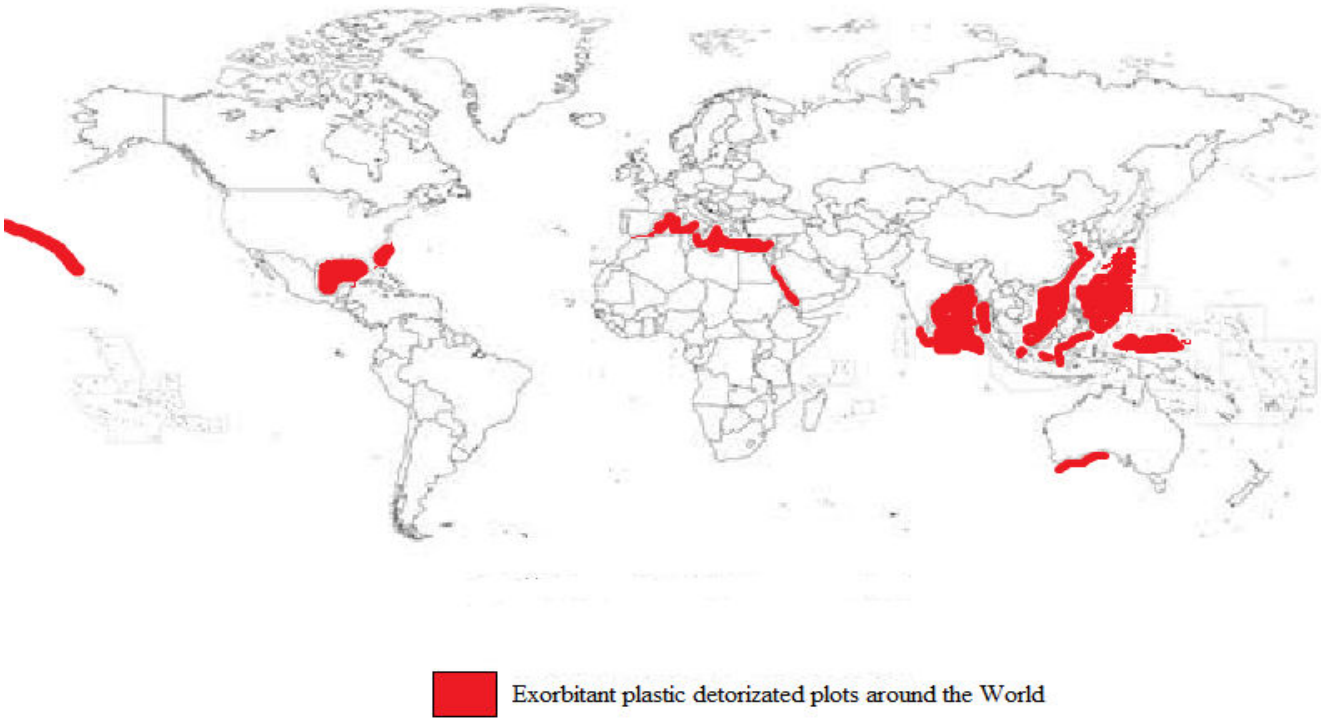

Figure 1. Plastic infected marine zones around the world.

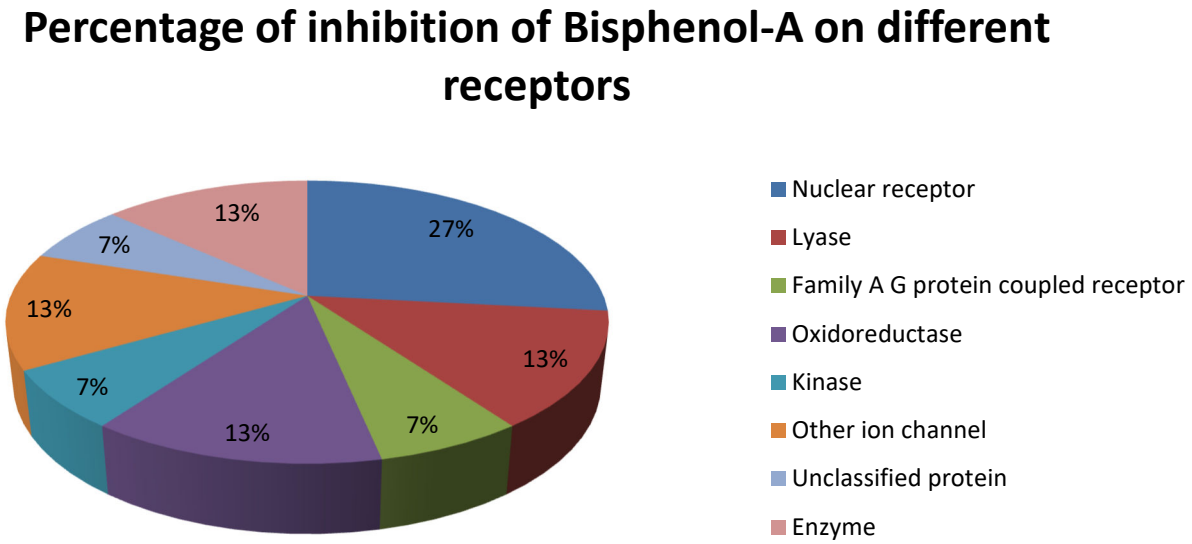

Figure 2. Percentage of inhibition of Bisphenol-A on different receptors.

Bisphenol-A has got a astounding potential of binding to different nuclear receptors and inducing their functions by inhibitions. Some of the receptors and the ligand of attachments are mentioned in the table. [26]

Table 1. Inhibitory actions of Bisphenol-A on three foremost receptors in the human anatomy [26].

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability	Known actives (3D/2D)
Androgen Receptor	AR	P10275	CHEMBL1871	Nuclear receptor	1	27 / 11
Estrogen receptor alpha	ESR1	P03372	CHEMBL206	Nuclear receptor	1	235 / 84
Estrogen receptor beta	ESR2	Q92731	CHEMBL242	Nuclear receptor	1	234 / 82

In the above mentioned table (Table 1)we can spot that Bisphenol-A is attacking the nuclear receptors of androgen and estrogen families and also the serotonin families where the action is concentrated around A G protein-coupled receptors .The degree of bindings varies among the compounds.(Fig 2)[26]

(Aloisi et. al. ,2001) did a study on the effect of Bisphenol-A on estrogen receptor alpha, and in this study the rats were chosen as the experimental group.The case and control groups were chosen as lactating and non lactating females .It is detected that Bisphenol-A is inducing and ameliorating ER immunoreactive cells discounting lactating rats. On the other hand, an interesting consequence is noted when the Bisphenol-A inhibited the action of ER immunoreactive cells in the arcuate nucleas in the lactating rats. [27]

(Teng et. al.,2013) found that though Bisphenol-A got a flair chance of locking with androgen receptors but the extent of locking is poor, resulting in low effect on androgen receptors. In this paper, we have employed several toxicological estimations softwares including molecular docking softwares which can determine the level of toxic manifestation by Bisphenol A. [28]

2. METHODOLOGY

2.1. Toxicity Analysis

In the contemporary paper, the research work was done mainly through literature reviews and series of software analysis which run under a pre input algorithm. At first, the chemical moiety under consideration was searched in Pubchem database, and notable information like its CAS no., SMILES and molecular structure were taken into account .[18]This information are vital providing the toxicity details of the said compound. QSAR modelling software enabled with a 2D descriptor (T.E.S.T, Version 4.1) was manoeuvred for this operation (USEPA, 2012).[29]The dry lab run was implemented to predict the acute toxicity by experimenting in vitro LC50 in Daphnia magna, LD50 in rat via oral route ,IGC50 study in T.pryreformes , and mutagenicity study in T. Typhimurium according to the protocol of the software. [29]

The corollaries of the analysis along with bioaccumulation factor and mutagenecity study were triaged and put up with the secured predictive data of Bisphenol-A from T.E.S.T. software. The results were secured with the utilization of consensus method, which encompasses the mean prognosticated LC50, LD50 , bioaccumulation factor, and mutagenicity values, and were procured from inbuilt QSAR algorithm. By abiding the concord of operation of the application, the structure of Bisphenol-A can be obtained through inputting the respective CAS registry no. The predicted value is derived according to the algorithm of the software.[29]

Toxicity prognostication in our experiment has followed the consensus methodology, which covers the process of obtaining empirical toxicity analysis from other QSAR methodologies, and a standard calculation is executed. This process usually gives the most correct consequences cause on error value will be abstained by other values which are all accepted into account. [29]

Further toxicity testing of Bisphenol-A were executed with the utilization of FDA model of Rat Oral LD50 .FDA model is chiefly contrived on the ground of experimenting a particular compound of interest using a cluster which has got structurally similar compounds segregated from the training set .(Martin et. al, 2016) made an equation on the training prototype by using a series of compounds, all of which got a cosine similarity coefficient of 75% with the chemical put on the test. That cosine similarity coefficient is expressed as SCi,k, [29]

$$SC_{i,k}=\frac{\sum_{j=1}^{\#descriptors} x_{ij}\ x_{kj}}{\sqrt{\sum_{j=1}^{\#descriptors} x_{ij}^2}\sqrt{\sum_{j=1}^{\#descriptors} x_{kj}^2}}$$

Where,

x_{ij} is the value of the jth normalized descriptor for chemical i (normalized with respect to all the chemicals in the original training set) [29] x_{kj} is the value of the jth descriptor for chemical k. [29]

The QSAR set got potential predictive power when the stated parameters are satisfied

$$q^2 > 0.5$$

$$R^2 > 0.6$$

$$\frac{(R^2 - R_o^2)}{R^2} < 0.1 \text{ and } 0.8 \leq k \leq 1.15$$

Where,
q^2= the correlation coefficient of the training set excluding one compound
R^2=correlation coefficient between observed and predictive toxicities of the test set
R_o^2 = correlation coefficient between observed and predictive toxicities of the test set with the Y-intercept calibrated to zero [29]
Other softwares are also utilized for the detection of toxic manifestation. Analysis on Swiss ADME was executed to detect the lipophilicity, drug likeliness and pharmacokinetics of the compound in interest [30]

2.2. Assortment of Ligand and Macromolecule

The crystalline three-dimensional (3-D) fabrication of Ligand Bisphenol-A (PubChem CID: 6623) along with Macromolecules Estrogen Receptor Beta (PDB ID:1L2J) ,Estrogen Receptor Alpha (PDB ID:1L2I) and Androgenic Receptor (PDB ID: 1GS4) were captured from the website of PubChem (https://pubchem.ncbi.nlm.nih.gov/) and protein data bank (http://www.rcsb.org).[18][31] The structures were taken maintaining the ententes of the wwPDB validation report.This structure was provided on based of X-ray Diffraction method of 2.0 Å.
Docking analysis was done with the help of Mcule 1-Click docking [32]

3. RESULTS

3.1. Toxicity Analysis

Scrupulous analysis through has relieved that Bisphenol-A is a mild toxic agent affecting numerous receptors and protein structures and altering the biochemical mechanisms of the body. CAS no. and molecular structures were chosen to detect to toxic manifestation of Bisphenol-A in various in silico macrocosm and the results were juxtaposed with the threshold limit. The analysis were done in T.E.S.T.(version 4.1.),SWISS ADME .[29][30]

T.E.S.T. analysis through FDA and consensus models were done for analysis of following parameters of Bisphenol-A.[29]

- Fathead minnow LC50 (96 hr)
- Daphnia magna LC50 (48 hr)
- T. pyriformis IGC50 (48 hr)
- Oral rat LD50
- Bioaccumulation Factor
- Mutagenecity

Predicted Fathead minnow LC50 (96 hr)analysis from Consensus method (Table 2) found to be 3.01 , Predicted Daphnia magna LC50 (48 hr) analysis from Consensus method(Table 2) found to be 1.73 , Predicted T. pyriformis IGC50 (48 hr) analysis from Consensus method (Table 2) found to be 5.57, Predicted Oral rat LD50 for 80-05-7 analysis from Consensus method(Table 2) found to be 3196.23. A lower value signifies more toxic outcome.

Table 2. In-silico predicted toxicity test of Bisphenol- A on different animal model.

Prediction results		
Endpoint	**Experimental value (CAS= 80-05-7) Source: ECOTOX**	**Predicted value**
Fathead minnow LC_{50} (96 hr) - Log10(mol/L)	4.69	4.88
Fathead minnow LC_{50} (96 hr) mg/L	4.65	3.01
Prediction results		
Endpoint	**Experimental value (CAS= 80-05-7) Source: ECOTOX**	**Predicted value**
Daphnia magna LC50 (48 hr) - Log10(mol/L)	**4.30**	**5.12**
Daphnia magna LC50 (48 hr) mg/L	**11.42**	**1.73**
Prediction results		
Endpoint	**Experimental value**	**Predicted value**
T. pyriformis IGC50 (48 hr) - Log10(mol/L)	**N/A**	**4.61**
T. pyriformis IGC50 (48 hr) mg/L	**N/A**	**5.57**
Prediction results		
Endpoint	**Experimental value (CAS= 80-05-7) Source:** ChemidPlus	**Predicted value**
Oral rat LD50 -Log10(mol/kg)	**1.85**	**1.85**
Oral rat LD50 mg/kg	**3247.32**	**3196.23**

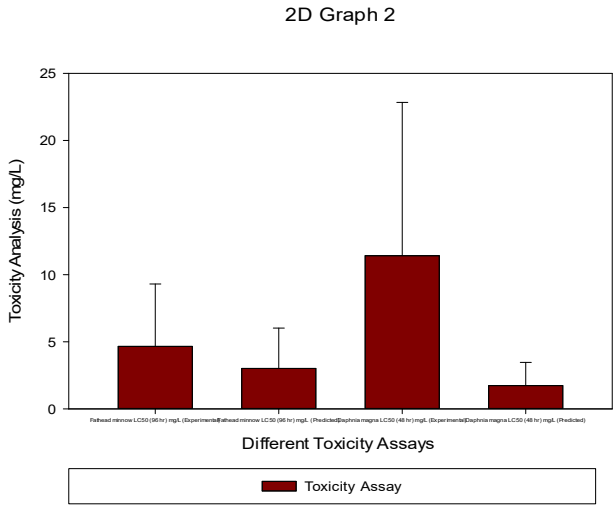

Figure 3. LC50 toxicity analysis.

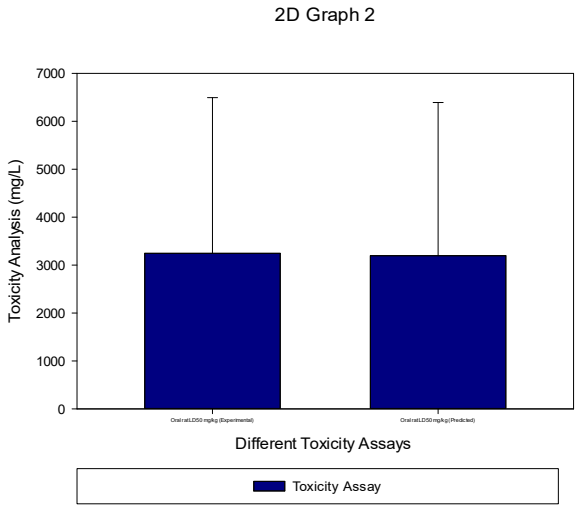

Figure 4. LD50 toxicity analysis.

The above table (Table 2) denotes the extent of toxic manifestations of Bisphenol-A in LC50, LD50 and IGC 50 test. In these tests, it is seen that the LC50 and IGC 50 tests showed toxic effects (lower values of doses) of Bisphenol-A. It may be possible that the aqueous solution of the compound may show more action due to additive effect. LD50 test showing lower toxicity (higher dose quantity) may also happen if Bisphenol-A show high affinity of lipid storage, manifesting lower value. Table shows the lipophilicity of Bisphenol-A. (Table 3)[30]

Table 3. Lipophilicity of Bisphenol-A [30].

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.05
Log $P_{o/w}$ (XLOGP3)	3.32
Log $P_{o/w}$ (WLOGP)	3.42
Log $P_{o/w}$ (MLOGP)	3.20
Log $P_{o/w}$ (SILICOS-IT)	3.29
Consensus Log $P_{o/w}$	3.06

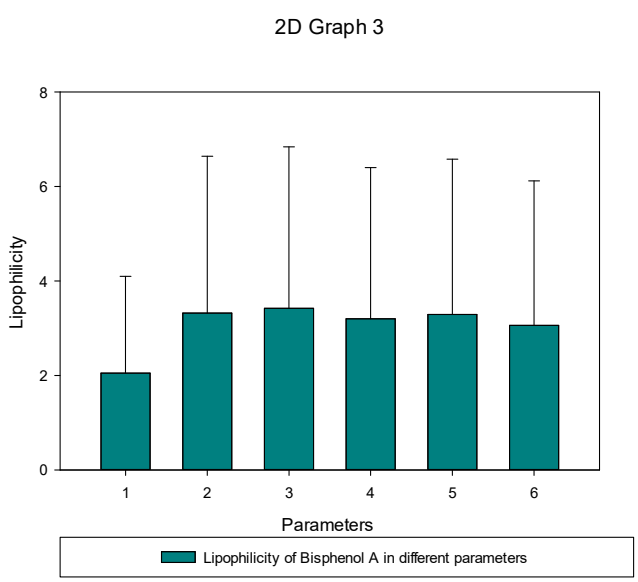

Figure 5. Lipophilicity at different parameters.

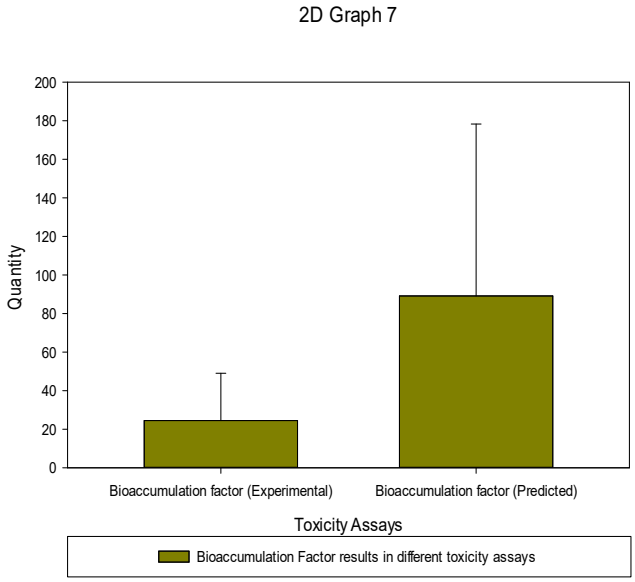

Figura 6. Bioaccumulation Factors.

(Experimental and Predicted)

Bioaccumulation factor of Bisphenol-A is found to be 89.15 (Table 4) and the log of value is found to be 1.95 with the FDA score r^2 equalling to 0.890(Table 5). Figure graphically represents the FDA model(Fig 3) .Mutagenicity estimation is seen to be negative with the predicted value of 0.15 with the sensitivity is found to be 1.000 (Table 7).

Table 4. Bioaccumulation factor study of Bisphenol-A.

Prediction results			
Endpoint	**Experimental value (CAS= 80-05-7) Sources: Dimetrov 2005, Arnot 2006, and Zhao 2008**	**Predicted value[a]**	**Prediction interval**
Bioaccumulation factor Log10	**1.39**	**1.95**	**1.23 ≤ Tox ≤ 2.67**
Bioaccumulation factor	**24.51**	**89.15**	**16.92 ≤ Tox ≤ 469.58**

Table 5. FDA model detection of Bisphenol-A.

Cluster model predictions and statistics					
Cluster model	**Test chemical descriptor values**	**Prediction interval Log10**	**r^2**	**q^2**	**#chemicals**
FDA model	**Descriptors**	**1.95 ± 0.72**	**0.890**	**0.832**	**30**

Table 6. FDA model of Bisphenol-A.

Parameter	Value
Endpoint	**Bioaccumulation factor**
r^2	**0.890**
q^2	**0.832**
#chemicals	**30**
Model	**FDA Model**

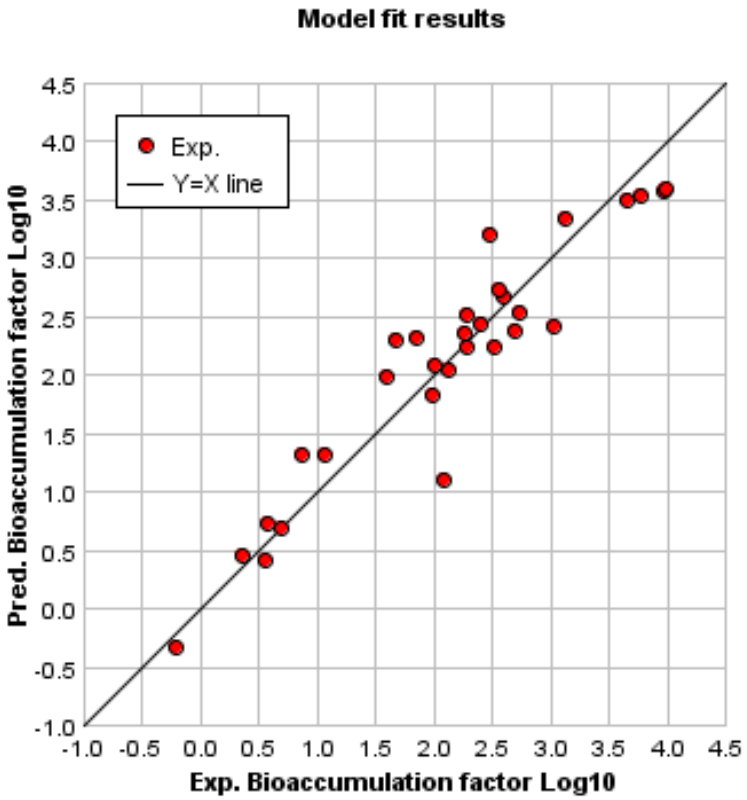

Figure 8. Graphical representation of the FDA model of Bisphenol-A.

Table 7. Mutagenicity analysis of Bisphenol-A.

Prediction Statistics				
Endpoint	Experimental value (CAS=80-05-7) Source: Toxicity Benchmark			Predicted Value
Mutagenicity value	0.00			0.15
Mutagenicity result	Mutagenicity Negative			Mutagenicity Negative
Prediction Statistics				
Endpoint	Concordance	Sensitivity	Specificity	#chemicals
Mutagenicity	0.933 (28 out of 30)	1.000 (10 out of 10)	0.900 (18 out of 20)	30

3.2. Molecular Docking

Bisphenol-A binds with Androgen Receptors and the binding axisses are X:0.5553, Y:31.5888 and Z: 4.6769 . It is seen that high binding affinity exists for Bisphenol-A-Androgen receptor complex, with maximum of -8.2 and minimum of -6.8.(Table 8)Negative score denotes high affinity .In figure , at A1 , we can detect the main binding protein residues are SER 71, TRP72 , GLY 74 and MET76 and this binding residues remained unaltered at rest three diagrams.(Fig 9)

Bisphenol-A binds with Estrogen Receptor Beta and the binding axisses are X:11.8689 ,Y:69.9637 and Z: 27.5956. We observe a towering binding affinity for Bisphenol-A with Estrogen Receptor Beta with the highest at -8.1 and lowest at -8.0(Table 9). At Figure, in A1 it is observed that the cardinal binding agent in TRP 68 along with CYS 67 in B1 and C1 with the faint presense of GLY 79 in B1 and C1 (Fig 10)

Binding of Bisphenol-A with Estrogen Receptor Alpha in shown in Table 10. It is detected that the binding axisses are X:5.48, Y:-0.0037 and Z:-5.492 with the maximum binding score at -8.2 and minimum at -7.8 . In this figure, the main binding agent is GLY 208 as seen in A1, B1 and D1 . ASN 206 , SER205 along with LYS 207 are also present, denoted in A1 and B1 .A posterior residue of MET 204 is detected in all of the sub figures (A1-D1) . (Fig 11)

Table 8. Binding centres and Binding affinities for Bisphenol-A and Androgen Receptors.

BISPHENOL-A and ANDROGEN RECEPTOR

BINDING CENTRE		
X Axiss	Y Axiss	Z Axiss
0.5553	31.5888	4.6769
Docking pose	**Docking score**	
#1	**-8.2**	
#2	**-7.7**	
#3	**-6.8**	
#4	**-6.8**	

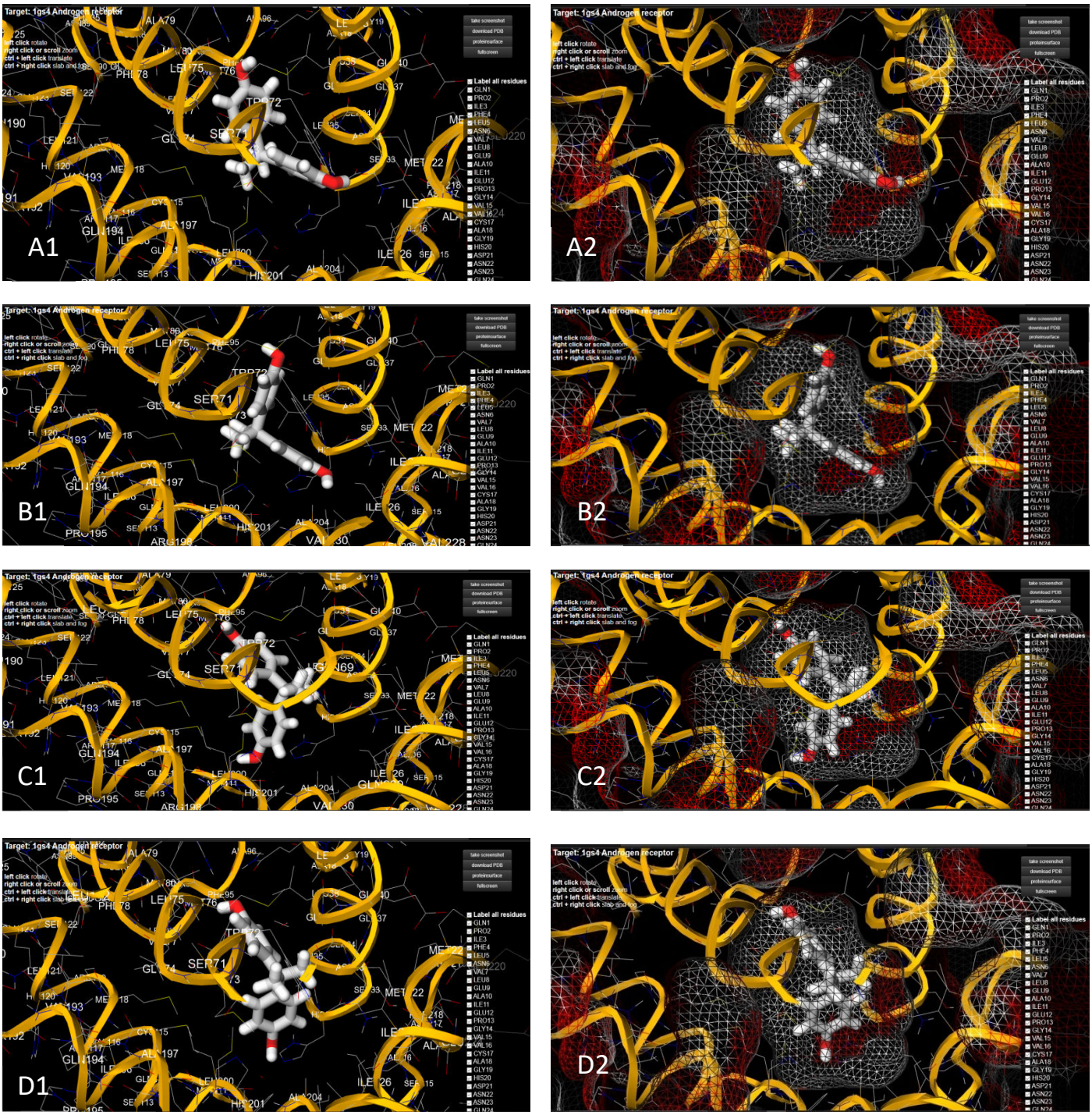

Figure 9. Bisphenol-A binding with Androgen Receptor.

Table 9. Binding centres and Binding Affinities for Bisphenol-A and Estrogen Receptor Beta.

BISPHENOL-A and ESTROGEN RECEPTOR BETA

BINDING CENTRE		
X Axiss	Y Axiss	Z Axiss
11.8689	69.9637	27.5956
Docking pose	**Docking score**	
#1	**-8.1**	
#2	**-8.0**	
#3	**-8.0**	
#4	**-8.0**	

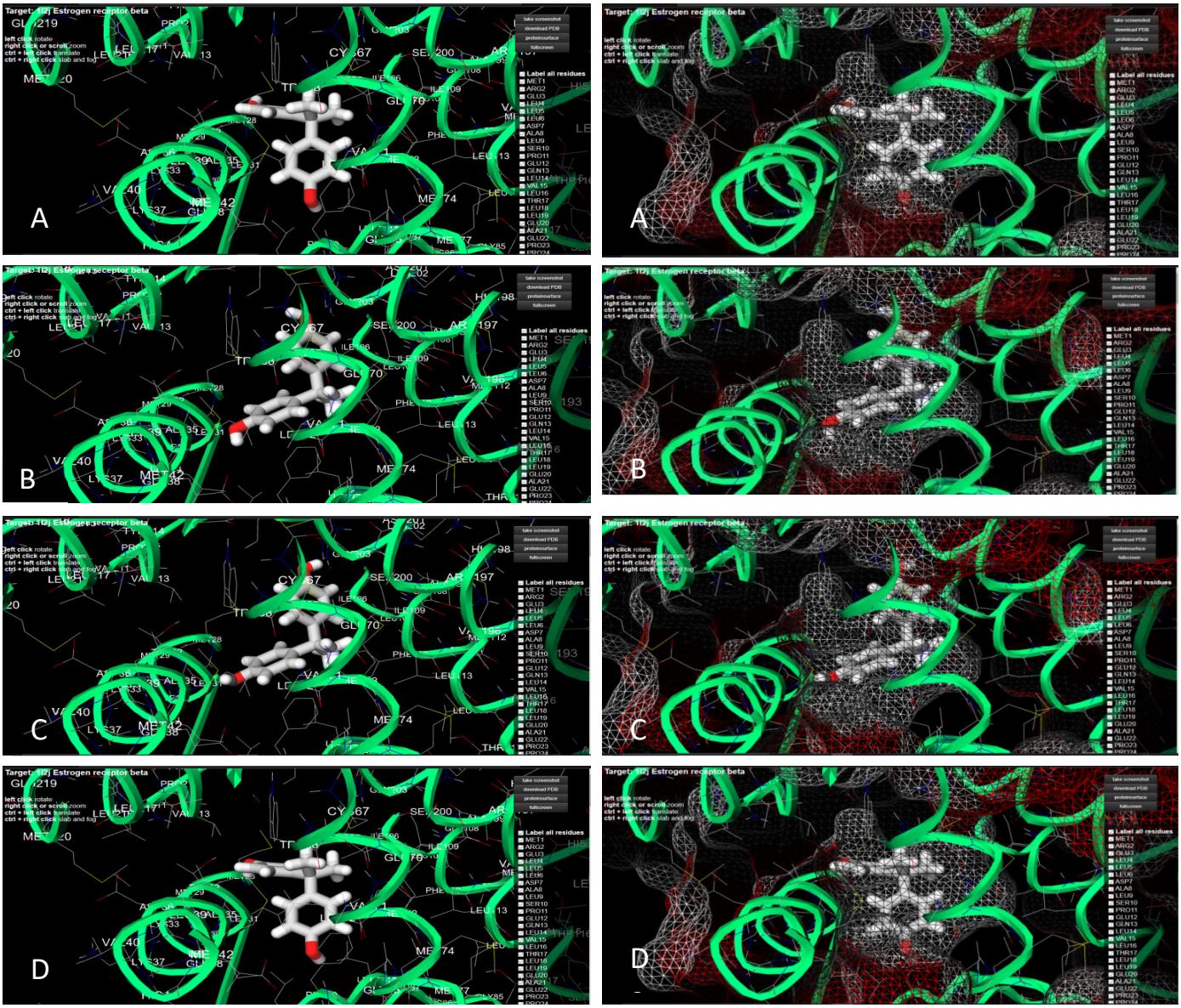

Figure 10. Bisphenol –A Binding with Estrogen Receptor Beta.

Table 10. Binding centres and Binding affinities for Bisphenol-A and Estrogen Receptor Alpha.

BISPHENOL-A and ESTROGEN RECEPTOR ALPHA

BINDING CENTRE		
X Axiss	Y Axiss	Z Axiss
5.48	-0.0037	-5.492
Docking pose	**Docking score**	
#1	**-8.2**	
#2	**-8.2**	
#3	**-7.9**	
#4	**-7.8**	

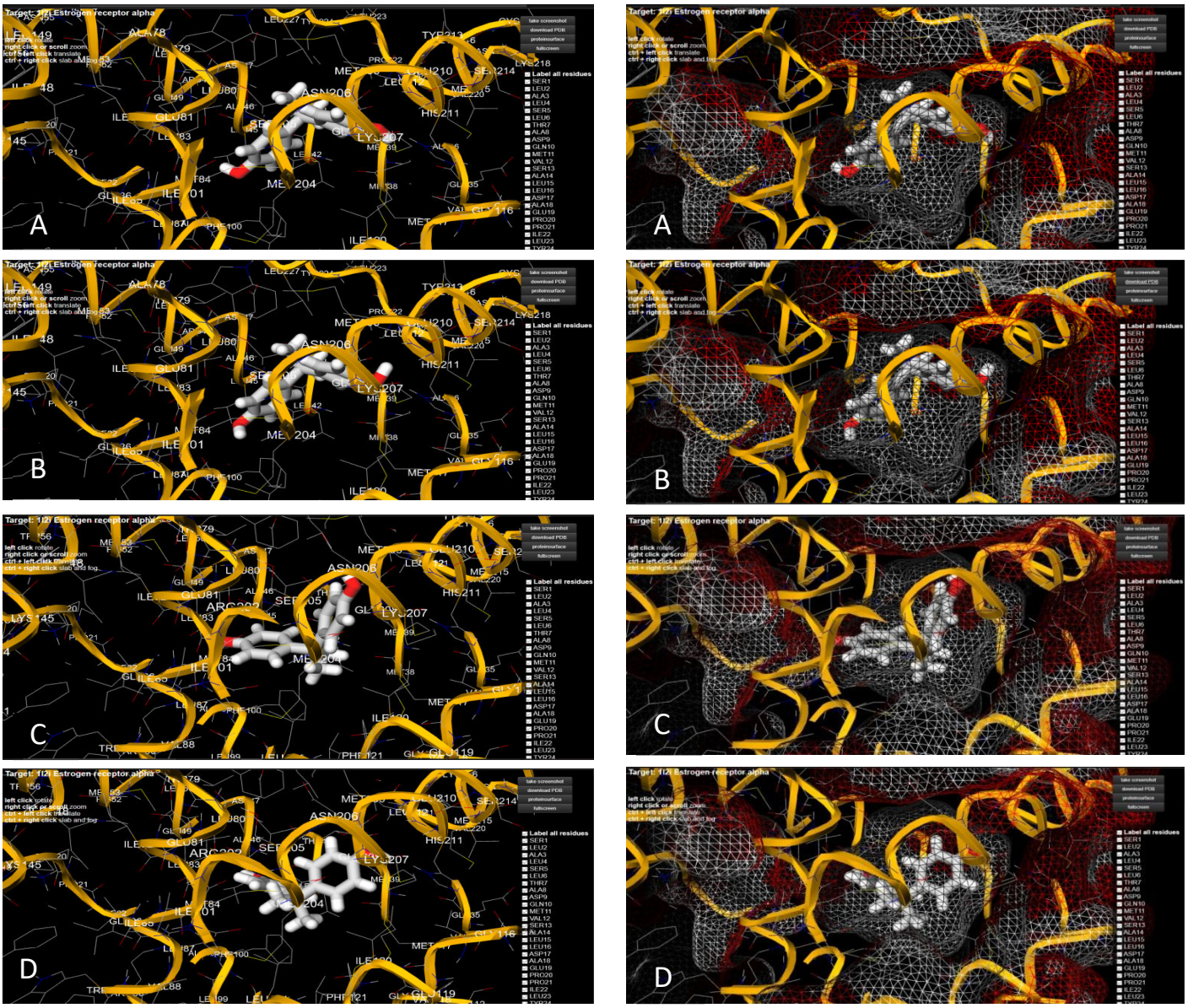

Figure 11. Bisphenol –A binding with Estrogen Receptor Alpha.

4. DISCUSSION

The above findings of the repercussion of Bisphenol-A are found to be quite pernicious to the biosphere and to the human anatomy. It is quite appalling to observe the extent of action done by this agent, which is quite common among our household accessories, not to mention to main facet of the containers from where we have our food and drink.Binding to the estrogen receptors are quite heinous cause these receptors controls the secondary sexual characters of the human female, and disruption of it got the highest potential of causing carcinogenesis.In silico toxicity analysis have proved to be significant since it is found that the LC50 is quite abnormal (lower value indicates more toxic outcomes) on *Daphnia sp.* and Fathead minnow .The main contradictory result was found on mutagenecity test, which have shown negative result .

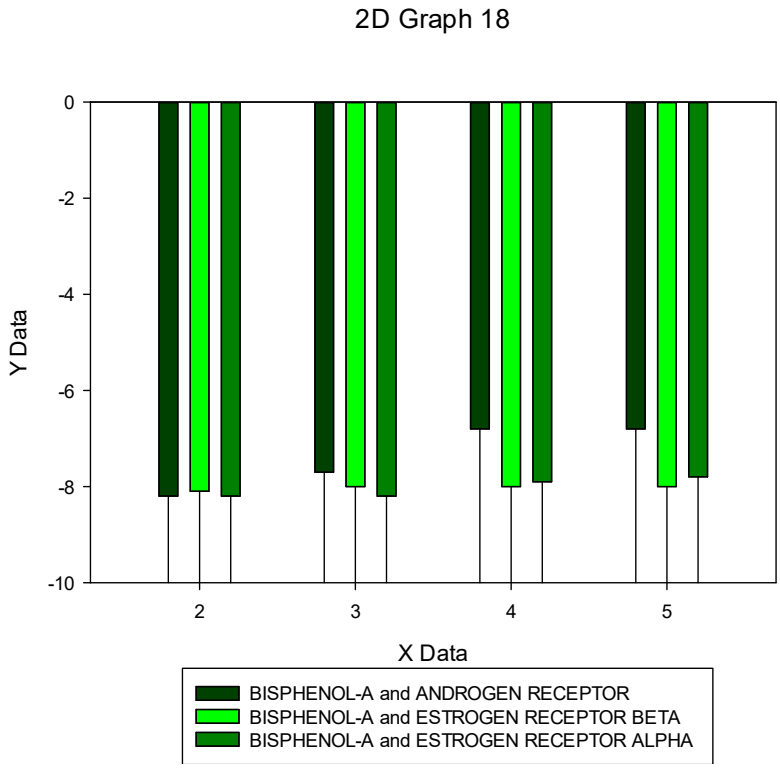

Figure 12. Different modes of binding reactions with the compounds. X data represents the number of modes, and Y data represents the binding energy.

5. CONCLUSION

Though Bisphenol-A is an cardinal facet of plastic, its effect on the living systems can't be disregarded, and exertions to be taken to replace the material off the market with a more eco-friendly one. Jute bags, utensils made from bagasse, vegetable-derived cutleries are gaining their popularity in this contemporary world. Their usage are currently at a feeble extent cause of lack of common awareness, lack of capitals for investing in this new products, etc. It is hopeful that the world would accept these products in a meteoric way.

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