1. INTRODUCTION

Existing as the vital source for Living systems, oxygen can sometimes act as a curse in disguise[1,2]. Oxygen atom lacks two electrons in its valence shell and bonds with atoms of same or different elements to achieve noble gas configuration[3].When this bond undergoes homolytic cleavage, the constituting atoms now possess unpaired electrons referred to as free radicals[4]. FR are highly reactive and serve as the initiators in almost every chain reaction occurring inside the body cells[5]. Because of the existence of unpaired electrons, these radicals have a potential to gain electrons and are called oxidants. In this way, the source from which they obtain electrons are antioxidants[6]. In the body, these oxidants are produced as ROS,RNS, RSS and RLS as a metabolic byproduct of aerobic respiration, cellular metabolism and immunogenic responses[2,7,8] . A disequilibrium is established when the natural defense system of the body gets overwhelmed with the exaggerate production of FR, leading to a condition known as Oxidative Stress[9,10].This sets the ground for ROS species to act upon the biological system thereby laying the foundation for any disease to take root inside the body[11].

The source of formation of ROS and RNS species may be endogenous or exogenous resulting in disturbed cellular homeostasis[1](**Figure 1**). The production of RLS is mediated either by enzymes, through LOX and COX activity or non-enzymatically via oxidation of PUFAs[7]. ROS and RNS species react with thiols to form RSS. These are comparatively less toxic although have tendency to damage proteins[2].ROS are majorly produced as an outcome of oxidative phosphorylation where an activated oxygen acts as a precursor for the formation of radicals [12]. O_2^- and OH• are generated under the influence of NOX4 enzyme, one of the seven oxidases of NOX family[10]. O_2^- gets reduced to H_2O_2 in mitochondria. H_2O_2 being the most ubiquitous of all, can also be yielded from peroxisomes via catalase activity[13,14]. OH• is considered as the most toxic species as it can damage almost anything around its formation site[15].

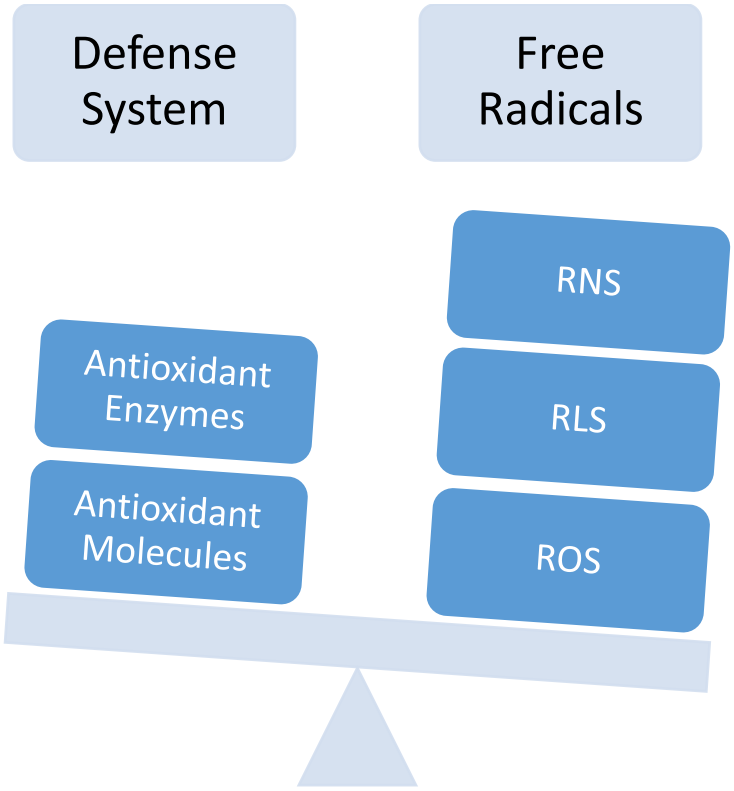


Figure 1: A disturbed homeostasis between oxidants and antioxidants: Oxidative Stress

The major catastrophic events that occur after the overproduction of ROS include (i) lipid peroxidation, hampering the lipid bilayer affecting the permeability and fluidity of membrane; (ii) protein oxidation, by formation of crosslinks, misfolding, production of carbonyl function account for proteasomal degradation; (iii) DNA damage, ss and ds breaks, modification of bases [16]. Studies show that excessive production of ROS bring about the activation of (ERK)1/2, PKB and PTK pathways [17].Metals such as Fe, Cu, Mn, Zn and Mg are also reported to participate in free radical production eventually leading to oxidative stress [18].

2. LITERATURE REVIEW

2.1 Vulnerability of brain towards Oxidative Stress

Oxygen requirement of the brain is as high as 20 percent of the total utilization within the body and therefore brain cells, particularly neuronal cells, because of their non-dividing nature, are very much prone to the attack of various oxidants [19]. The presence of metals like Fe, Cu initiate bountiful production of ROS and high levels of PUFAs in the cell membranes increases its susceptibility to lipid peroxidation[20]. ROS catalyze several cascades that alter the permeability of blood-brain barrier leading to inflammation and apoptosis[21]. They also attack the neurons by facilitating the generation of DNA-protein adducts by oxidizing these molecules[22]. However, this effect of ROS is not same throughout the brain due to presence of neuronal diversity causing selective vulnerability to oxidative stress. Such impuissant neurons fall prey to ROS causing ageing, several neurodegenerative disorders such as Alzheimer's and Parkinson's disease and eventually cell death[23]. Hippocampus being the favorite one, amygdala, cerebellar granule cells and prefrontal cortex represent the easy target sites of attack of ROS, provoking neurotoxicity. This leads to series of reactions in the CNS resulting cognitive and behavioral impairment[12]. Microglia cells are the macrophages of brain responsible for the removal of unwanted or defected cells by phagocytizing them simultaneously secreting O_2^- via NOX2, therefore the production of these radicals would depend upon local O_2 availability[24]. In a similar manner, occurs auto-oxidation of neurotransmitters where oxygen interacts with dopamine to form a semiquinone radical which again reacts with another oxygen molecule in the vicinity to release O_2^-[25] .Here, the formation of this superoxide radical can be further catalyzed by the interference of bioactive metals which are present in ample quantity in brain[26,27].Another factor responsible is disrupted redox homeostasis as an outcome of weak endogenous defense system. For example, neurons are endowed with $1/50^{th}$ of the catalase content as compared to that of hepatocytes for H_2O_2 removal[28,29]. In sum, brain is highly inclined to get affected by oxidative stress easier than any other part of the body.

2.2 Oxidative Stress Mediated Neurodegeneration

Neurodegenerative disorders are the set of diseases attributed by progressive loss of neurons [30,31]. Oxidative stress is consistently linked with neurodegeneration but the etiology of neuronal degradation is still unknown[32]. The incapacitation of endogenous defense antioxidant system to cope up with incessant generation of free radicals gives rise to several diseases including Alzheimer's Disease(AD), Parkinson's Disease(PD), and Huntington Disease(HD) [8].

2.2.1 Alzheimer's disease

AD can be visualized as the outcome of various intraneuronal alterations serving as a foundation for cognitive and behavioral debility[33]. The formation of amyloid-β plaques is observed along with neurofibrillary tangles comprising of tau protein[34].The exact mechanism and etiology is unexplored yet but several details describe the disease: (i) aging[35], (ii) mitochondrial dysfunction[36], (iii) compromised immunity[37], (iv) impairment in blood-brain barrier[38], (v) genetic factors (ApoE4 gene), (vi) head injury, (viii) inappropriate diet and lifestyle[39], (ix) degradation of glutamate in the perforant pathway[40],(x) dropping levels of acetylcholine[41] and serotonin[42].

Studies provide evidences of the involvement of iron in senile plaques which already has a decisive role in ROS production[43].Several observations have been made regarding the enhanced peroxidation of lipids in the temporal lobes of brain[44,45] and this could be a possible reason for phospholipid asymmetry altering the cell membrane morphology[46]. MDA, $ONOO^-$ and heme oxygenase 1 levels were also found to be raised in the neurofibrillary tangles of the AD brain[47]–[49].A deteriorating effect of β-amyloid on neuronal cultures was seen which was more pronounced with H_2O_2[50,51]. DNA oxidation in peripheral blood cells and RNA oxidation is also observed in the cortex of the AD brain [52,53].

2.2.2 Parkinson's disease

It is the upshot of progressive decay of dopaminergic neuronal cells in nerve terminals of striatum and substantia nigra[54].The shortfall of dopamine causes dysfunctioning of the motor features(resting tremor, bradykinesia, rigidity, postural instability), non-motor features(depression, insomnia) and impairment of executive functions(problem solving, mental flexibility) which may not be noticed in early phases of the disease[55].

The extent of ROS production may hint upon the magnitude of its role in PD. Quinones and free radicals are the auto-oxidation products of dopamine which reorient themselves to form aminochrome and acts as a precursor to form O_2^- and neuromelanin[56,57]. Monoamine oxidase (MAO) are group of enzymes responsible for oxidative deamination, out of which MAO-B present in glial cells regulates dopamine metabolism[58]–[60]. One of the byproduct of MAO-B metabolism is H_2O_2 which is a small and uncharged radical, therefore can easily escape into the cell membrane catalyzing the formation of •OH[61,62]. Furthermore, GSH depletion in substantia nigra points towards the oxidative damage to dopaminergic neurons, as suggested by several studies[63]–[65]. A disturbance in the regulation of Ca^{2+} homeostasis may lead to extensive mitochondrial activity, further initiating ROS thereby causing insult to the nigral neurons[66]–[68].

2.2.3 Huntington's disease

It is a fatal degenerative disorder primarily affecting cerebral cortex, striatum and thalamus indicated by uncontrolled movements, loss of cognitive abilities and premature death[69]. Several hypotheses suggest oxidative stress as the primary event in the pathology of the disorder[69]–[71].Elevated levels of 8-OHDG[72](biomarker of DNA oxidation), cytoplasmic lipofuscin, MDA(lipid peroxidation product)[73,74], 3-nitrotyrosine[73]($ONOO^-$ induced oxidative stress marker) were observed in samples of HD brain. Pathological changes involve poly Q associated oxidative stress leading to neuronal cell death[75].

2.3 Natural Antioxidant Defense System

Nature has supported the living organisms with inbuilt antioxidant system to rectify the altered levels of oxidants and protect the cells from the wrath of exaggerated production of ROS[76].To overcome the imbalance of oxidants and antioxidants, the system possesses two

sets of protective mechanisms; viz ;defense enzyme system and low molecular weight antioxidant molecules[77]. To assist the fragile endogenous system, exogenous antioxidants from the dietary sources become vital to neutralize the effect of radicals[78].

2.3.1 Superoxide Dismutase (SOD)

The fundamental function of SOD is to convert highly reactive O_2^- into less toxic products, hydrogen peroxide and r oxygen[79].

$$2O_2^- \rightarrow H_2O_2 + O_2 \quad (2.1)$$

Superoxide Dismutase has three isoforms; (i) SOD1, for removal of superoxide from cytosol; (ii) SOD2, for eliminating superoxide from mitochondria; (iii) SOD3, for eliminating extracellular superoxide radicals[80].

Evidences suggest mutation in a gene encoding for SOD1 as a result of oxidative damage in some cases of ALS. Impairment in the expression of SOD is also involved in ischemia-reperfusion injury[81].

2.3.2 Glutathione Peroxidase (GPx)

This enzyme is universally present in both cytosol and mitochondria and is responsible for reduction of peroxide into water and alcohol respectively, under the influence of GSH[82].

$$ROOH + 2GSH \rightarrow ROH + H_2O + GSSG \quad (2.2)$$

In humans, there are eight isoforms of GPx, out of which five are selenium dependent and other three have cysteine instead of selenocysteine[83]. In brain, the major antioxidant enzyme present is GPx 1 which exists particularly in microglia[84].

2.3.3. Catalase (CAT)

Primarily present in peroxisomes, major role performed by catalase is the conversion of hydrogen peroxide into water and oxygen by utilizing Fe^{2+}/Mn^{2+}. Other places where CAT is found is cytoplasm and mitochondria[19].

$$2H_2O_2 \rightarrow 2H_2O + O_2 \quad (2.3)$$

In the etiology of PD, CAT is responsible for the activation of TRP cation channels and regulation of calcium ion influx caused due to oxidative damage in neurons[85].

2.3.4 Peroxiredoxins (PRx)

PRx are ubiquitous thiol specific peroxidases responsible for the neutralization of complete cytoplasmic and almost all mitochondrial hydrogen peroxide. They possess a cysteine residue in their active site for immediate reduction of peroxide[86].

It has six isoforms, three of them being located in both nuclei and cytoplasm (PRx 1, 2 and 4); PRx 3 in mitochondria and PRx 5 universally present[87]–[89].The levels of PRx 6 are found to be upregulated in Parkinson's frontal cortex suggesting compensatory response against cell death[90].

2.3.5 Glutathione

A tripeptide of glycine, cysteine, and glutamate; glutathione is an important enzyme for cell survival[80]. It is present in noticeably high concentrations in cells performing tremendous metabolic activity[91]. In the cells, the ratio of GSH (reduced) to GSSG (oxidized) maintains the redox status of a healthy cell. It has role in inhibiting apoptosis and oxidative damage mainly caused by superoxide and hydroxyl radicals[92].

GSH gets depleted in brain due to arachidonic acid through LOX activity and increased levels of phospholipase A_2 causing cellular damage[93].

2.3.6 Glutathione Reductase (GR)

It maintains glutathione in its reduced state by utilizing NADPH and FAD in the cells[94].Its working is highly sensitive and may get inactivated by $ONOO^-$ radicals[95].

2.3.7 Vitamins

Vitamin C and Vitamin E are well-known classical antioxidants for sustaining the integrity and functionality of the neuronal health[96,97].

2.4 Structure-Activity Relationship

SAR is an approach to establish the correlation between the structure and geometry of a molecule and its possible activity[98]. These have a great importance in pharmacological activity, toxicity, drug designing and pharmacophore modelling. The activity of a substance can therefore be represented as a function of its physicochemical properties[99].

Biological Activity = f(Physicochemical Property) (2.4)

The goal of SAR is to recognize the understanding of any molecule as an active or inactive compound and determining their relative activities and what similarity or dissimilarity in their properties sets them apart from the inactive compounds[100](**Figure 2**).

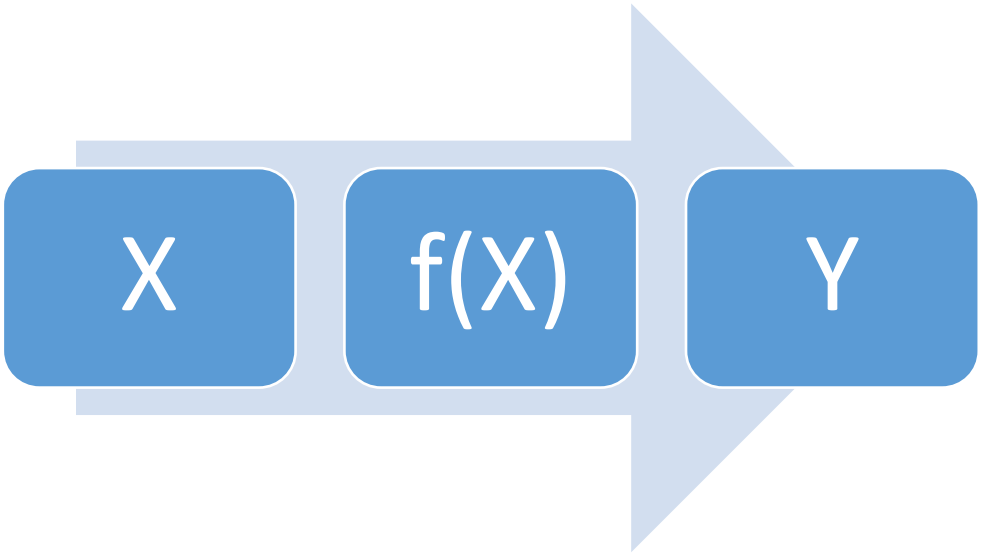


Figure 2: Basic concept of SAR: The predicted activity Y is a function of structural parameter X, where X is an independent variable and Y being a dependent variable.

The structural parameters or descriptors are the structural properties of the molecule which derive its relationship with the biological activity[101]. There can be thousands of molecular descriptors for a single molecule which are broadly the expository of their physicochemical properties, electronic properties, stearic properties, lipophilicity, hydrogen-bonding, shape, charge and polarizability. The parameters studied in this study include:

(a)Topological

(i) Path Walk Index

(b)Molecular

(i) Hydrophilicity, (ii) Molar Refractivity, (iii) Partition Coefficient

(c) Quantum-Chemical

(i) Dipole Moment

(d) Quantum-Mechanical

(i) Heat of Formation

(e) Constitutional Indices:

(i) Ionization Potential

(f)Electronic

(i) HOMO-LUMO Gap, (ii) Total Energy

Molar refractivity provides measure of how easily a molecule can be polarized and its volume. Partition Coefficient describes the hydrophobic character of the molecule[102]. Ionization Potential is the tendency to lose the valence shell electron. Heat of formation is the enthalpy associated with the formation of a molecule from its constituent atom and gives the measure of thermal stability of that substance. Dipole moment measures the strength and orientation behavior of a molecule in an electrostatic field[103]. HOMO is highest occupied

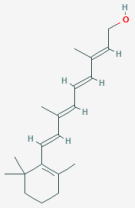
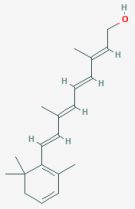
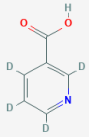
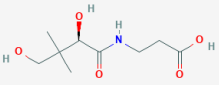
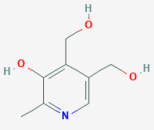
orbital and LUMO is lowest unoccupied orbital, LUMO being at higher energy level. The energy gap determines the ease of excitation of an electron from lower energy state to higher energy state[104].

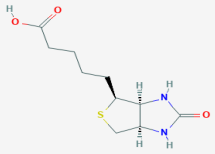
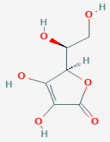
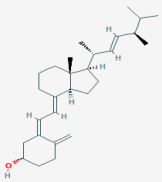
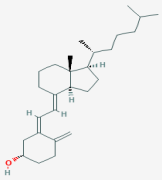
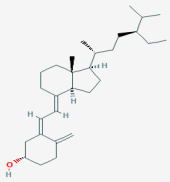
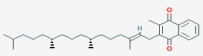
There are computational tools to predict the activity or inactivity of a compound based on these structural properties. These methods are helpful in understanding the interaction of biomolecules with different enzymes, cell membranes. Machine learning tools are employed in development of predictive models and potency of new and untested molecules or drugs can also be evaluated.

3. METHODOLOGY

3.1 Compounds Selection

Vitamins A1, A2, B3, B5, B6, B7, C, D2, D3, D5, E, K1, K2 and K3 were selected for screening purpose from PubChem database (https://pubchem.ncbi.nlm.nih.gov) (**Table 1**).

Vitamin	Chemical Name	Structure	Pub_Chem_Id	Molar Mass(g/mol)
A1	Retinol		445354	286.459
A2	Dehydroretinol		6436043	284.443
B3	Nicotinic-d4 Acid		12198448	127.135
B5	Pantothenic Acid		6613	219.237
B6	Pyridoxine		1054	169.18

B7	Biotin		171548	244.309
C	Ascorbic acid		54670067	176.124
D2	Ergocalciferol		5280793	396.659
D3	Cholecalciferol		5280795	384.648
D5	Sitocalciferol		9547700	412.702
E	Tocopherol		14985	430.717
K1	Phylloquinone		5284607	450.707

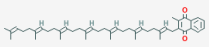
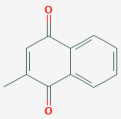
K2	Menaquinone		5287554	649.016
K3	Menadione		4055	172.183

Table 1: Selected Vitamins and their 2-D molecular structures

3.2 Descriptors Calculation

Descriptors were computed by using :(i)E-DRAGON (version 1.0) software by Prof. Todeschini and Consonni[105] and,(ii)Turbomole (version 4.4.1) software developed by Prof. Reinhart Ahlrichs[106] for a set of 14 vitamins for screening (**Table 2**) . Memantine and Pramipexole, well known drugs for Alzheimer's and Parkinson's disease are chosen to be controls for the comparison of descriptor values of vitamins with them.

Program	Descriptor	Type	Description
DRAGON	PW2	Topological	Path/walk shape indices
DRAGON	Hy	Molecular Properties	Hydrophillic factor
DRAGON	AMR	Molecular Properties	Molar Refractivity
DRAGON	ALOGP	Molecular Properties	Partition Coefficient
TMoleX	μ	Quantum-Chemical	Dipole Moment
TMoleX	H_f	Quantum-Mechanical	Heat of Formation
TMoleX	I.P	Constitutional Indices	Ionisation Potential

Table 2: List of Descriptors along with the employed program

3.3 Geometry Optimization

Geometry optimization is performed in order to achieve ground state stationary point where the net force on every atom is minimal. We have used here MOPAC program for optimization[106,107].

3.4 DFT Analysis

Density Functional Theory is one of most reliable and widely used method for calculating quantum chemical properties, thermodynamics and kinetics of a molecule in general conditions. Additional descriptors like dipole moment, H-L Gap, and total energy were calculated by this method using Turbomole software.

3.5 To check Blood-Brain Permeability

Blood-Brain Permeability was checked by using BBB Predictor tool (https://www.cbligand.org/BBB)[108].

3.6 Activity Prediction

To anticipate the biological potential of any compound including toxicity, pharmacological effects and mechanisms PASS tool is employed[109]. Based on the Structural Activity Relationship, it gives the probability of a compound to be active or inactive for a particular biological mechanisms. We have used this software to predict the activity spectra of the selected vitamins (if any), all of which are associated with neurodegeneration:

(i)Lipid Metabolism Regulator Activity

(ii)Antioxidant Activity

(iii)Nitric Oxide Antagonist Activity

(iv)Arachidonic Acid Antagonist Activity

(v)Cytochrome P450 stimulant Activity

(vi)Heme Oxygenase Stimulant Activity

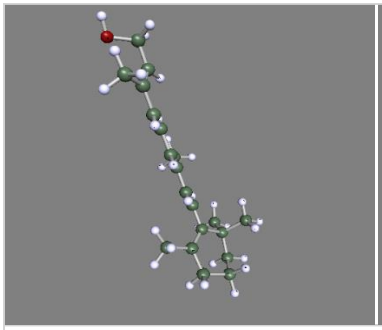
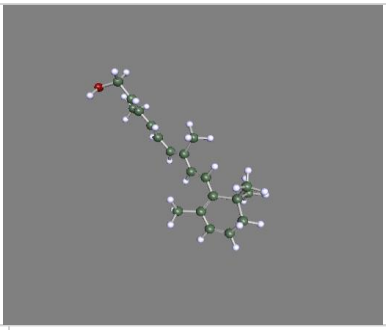
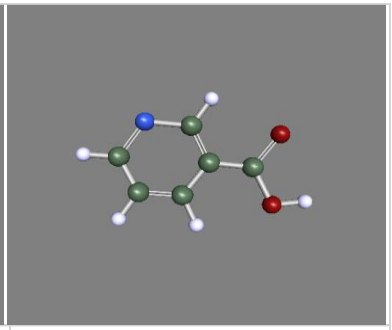
(vii) Antihypoxic Activity

3.7 Docking

The Vitamin/Vitamins showing maximum biological potential with best suited set of predicted activity(and possessing maximum stability) and calculated descriptors are chosen for docking with 12-Lipoxygenase, a well-known intermediate of arachidonic acid metabolism, which upon activation induces oxidative stress and cell death. SDF files of the ligands were taken from PubChem Database. Conversion of the SDF files to PDB format was achieved by using OpenBabel tool. The PDB structure of 12-LOX was obtained from ProteinDataBank (https://www.rcsb.org)[110]. The active site prediction of the protein was done by Scfbio, IIT Delhi (http://www.scfbio-iitd.res.in)[111]. The ligand and target files were imported to SwissDock web server for docking[112]. Molecules possessing lowest energy tend to have higher affinity towards a protein.

4. RESULTS

4.1 Geometry Optimization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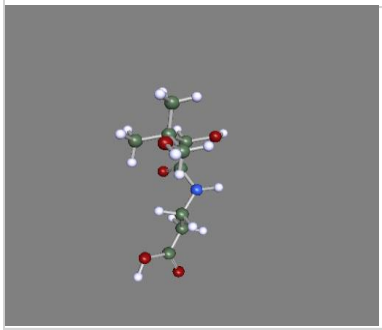
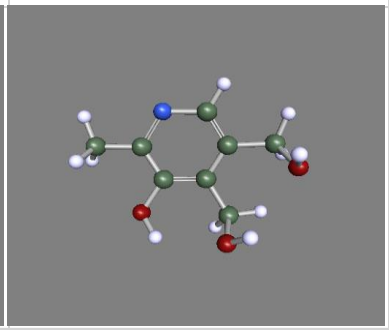
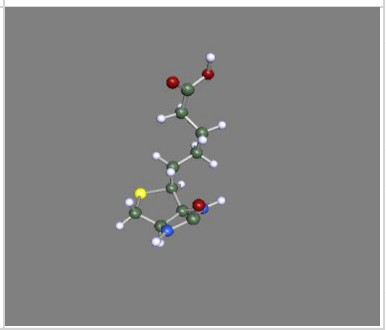
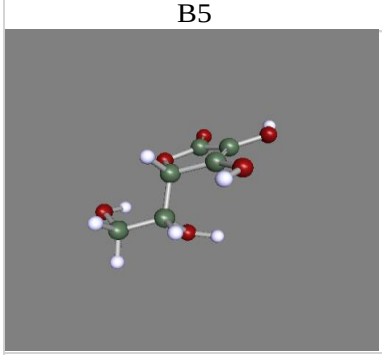
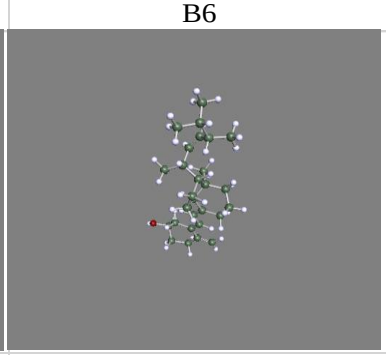
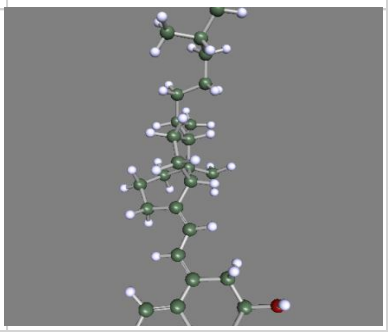
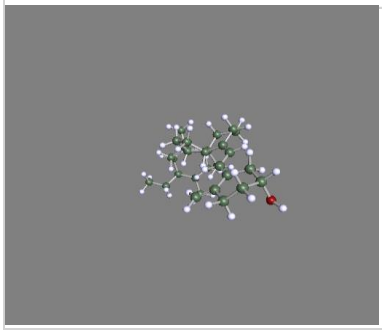
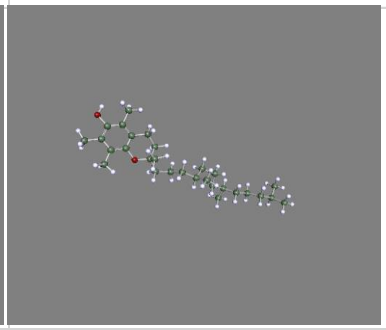
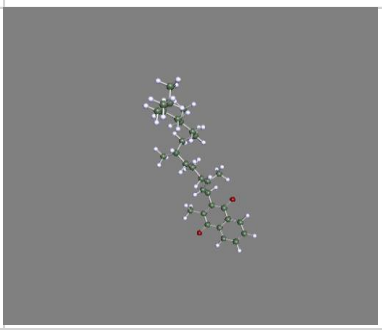
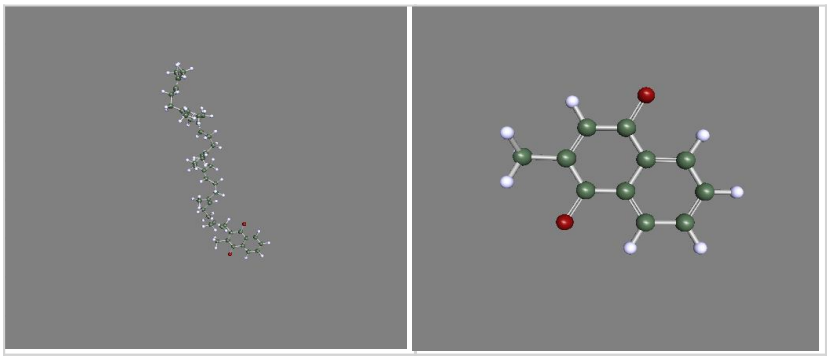
		
B5	B6	B7
		
C	D2	D3
		
D5	E	K1



K2	K3

Figure 3: MOPAC optimized geometry of molecules [Color Code: Green-Carbon, White-Hydrogen, Red-Oxygen, Blue-Nitrogen]

Geometry optimization aims at adjusting the geometry so as to lower the overall energy of the molecule thereby achieving the most stable conformation within which the force experienced by each molecule would be minimum. Therefore, the stable conformations of the each vitamin is achieved (**Figure 3**).

4.2 Descriptor Calculation

Vitamin	PW2	ALOGP	Hy	AMR	μ	H_f	IP	H-L Gap	E_{TOTAL}
A1	0.571	5.317	-0.479	97.923	1.139	-30.654	8.243	2.006	-854.685
A2	0.571	4.872	-0.479	99.04	1.562	-1.199	8.275	1.774	-853.469
B3	0.556	0.284	-0.001	30.66	3.153	-57.534	10.419	3.343	-436.558
B5	0.585	-0.977	2.35	51.586	2.323	-248.719	10.359	4.36	-783.505
B6	0.567	-0.514	1.555	43.819	2.469	-123.418	9.231	3.692	-591.452
B7	0.572	0.645	1.372	59.967	3.034	-129.253	8.875	4.469	-1123.52
C	0.592	-1.759	2.698	36.459	4.227	-233.141	9.879	3.718	-684.274
D2	0.597	7.563	-0.541	128.889	1.203	-56.511	8.401	2.865	-1167.73
D3	0.589	7.756	-0.535	123.224	1.268	-86.247	8.457	2.87	-1129.68
D5	0.591	8.464	-0.547	132.373	1.171	-90.365	8.28	2.911	-1208.24
E	0.589	10.416	-0.52	135.086	2.672	-178.848	8.323	3.573	-1284.68
K1	0.572	10.251	-0.931	142.957	0.733	-115.005	9.46	1.725	-1358.43
K2	0.566	14.981	-0.953	216.915	1.446	-49.026	9.039	1.249	-1940.31
K3	0.591	2.204	-0.822	50.615	0.986	-23.245	10.215	1.954	-574.039
Memantine	0.648	1.908	0.38	54.485	1.092	-43.061	9.681	5.631	-524.296
Pramipexole	0.56	1.384	1.383	61.488	1.308	13.701	8.692	3.182	-953.266

Table 3: Calculated values of Descriptors for Vitamin molecules and Controls

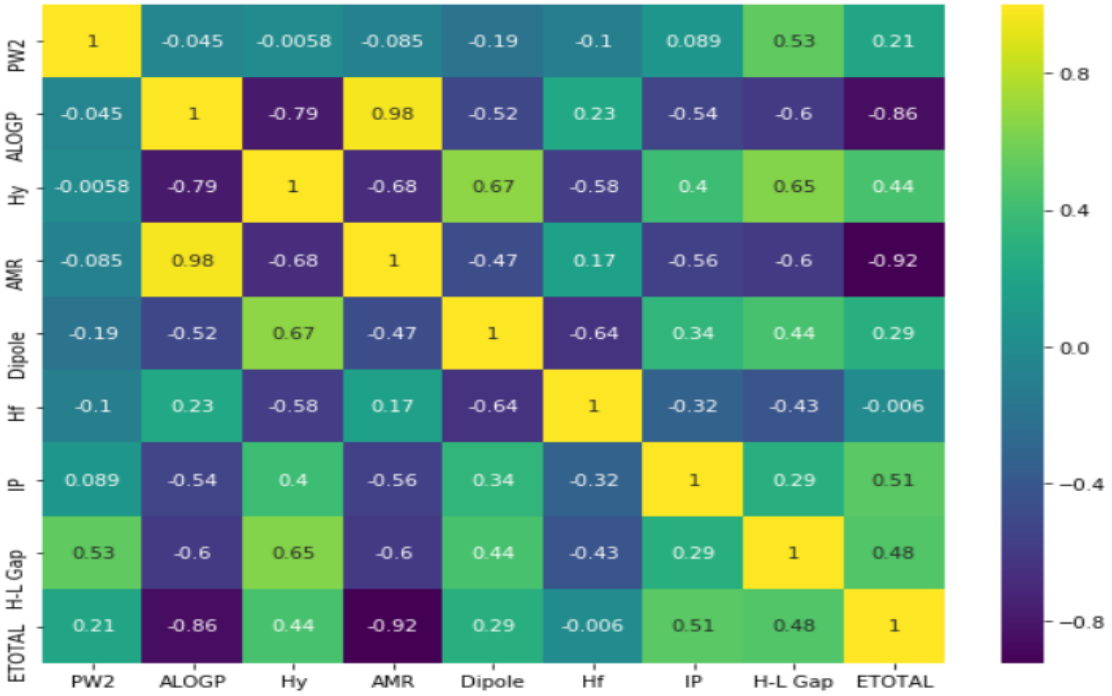


Figure 4: Heat map showing the correlation among various descriptors

Descriptors were successfully computed (**Table 3**) for a list of vitamins and correlation among them is also checked (**Figure 4**).

4.3 Prediction of Activity Spectra

Vitamins	AO	LMR	NOA	AAA	CP450S	HOS	AH
A1	0.708	0.953	0.248	0.225	0.713	0.078	
A2	0.584	0.87	0.222	0.224	0.721	0.062	0.242
B3	0.749	0.811	0.556	0.212	0.242		0.389
B5	0.616	0.954		0.181			0.538
B6	0.547	0.479	0.204	0.186	0.244		0.323
B7	0.436	0.426	0.433				
B8	0.436	0.426	0.433				
C	0.951	0.963	0.204	0.205			0.37
D2	0.254	0.266	0.155	0.194	0.252	0.07	
D3	0.183	0.305	0.301	0.239	0.388	0.068	
D5	0.167	0.258	0.272	0.223		0.065	
E	0.968		0.471	0.202	0.536		
K1	0.611	0.483	0.306	0.224	0.298		
K2	0.685	0.541	0.57	0.246	0.401		
K3	0.254	0.486	0.272	0.223			
AO=Antioxidant; LMR=Lipid Metabolism Regulator; AAA=Arachidonic Acid Antagonist; NOA=Nitric Oxide Antagonist; CP450S= Cyt P450 Stimulant; HOS=Heme Oxygenase Stimulant; AH= Antihypoxic							

Table 4: Activity Spectra of the Vitamin molecules

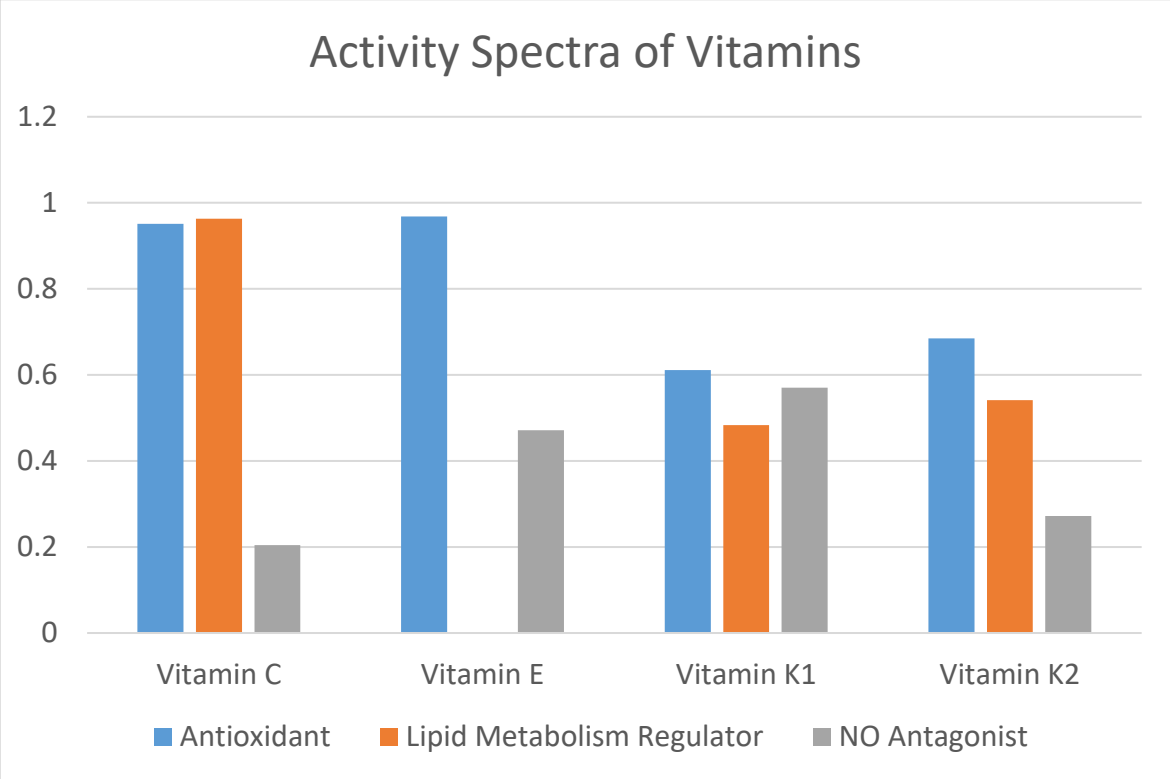


Figure 5: Graphical Representation of Activity Spectra of selected Vitamin molecules

Using PASS tool, activity spectra of the molecules was computed (**Table 4**), (**Figure 5**).

4.4 Blood-Brain Barrier Permeability

All Vitamin molecules were found to be BBB permeable, except Vitamin B5.

4.5 Electrostatic Potential

Electrostatic Potential maps facilitate the visualization of charge distribution of the molecules. They are implemented in analyzing the behavior of complex molecules, geometry and possible reactivity towards an electrophile or a nucleophile. Based on electronegativity difference, the color code for the map is as follows:

Blue > Green > Yellow > orange > Red (positive to negative) (**Figure 6)**

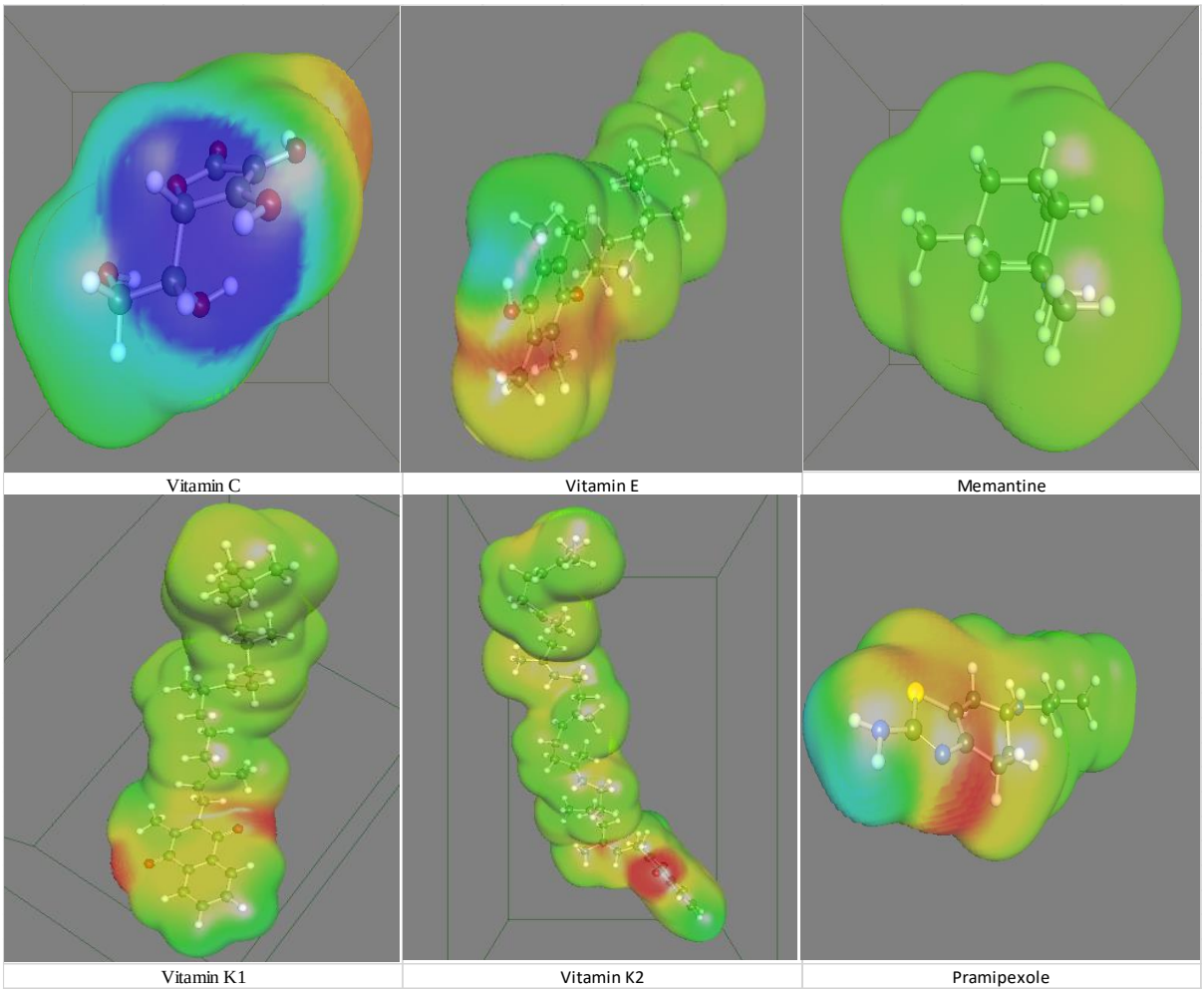


Figure 6: Electrostatic Potential Map for Vitamin C, Vitamin E, Vitamin K1,Vitamin K2, Memantine and Pramipexole

4.6 Docking

Cavity	Residue	Cavity Point	Volume (cubic Å)
1	Tyr	(0.07,7.92,1.93)	142
2	Trp	(-20.24,18.96,29.66)	115
3	Tyr	(-32.03,7.16,33.54)	77
4	Phe	(-5.81,-19.36,-0.66)	70
5	Ser	(-35.45,-7.48,32.62)	90
6	Leu	(-4.48,-4.43,4.44)	74

Table 5: Active Site Prediction for 12-Lipoxygenase

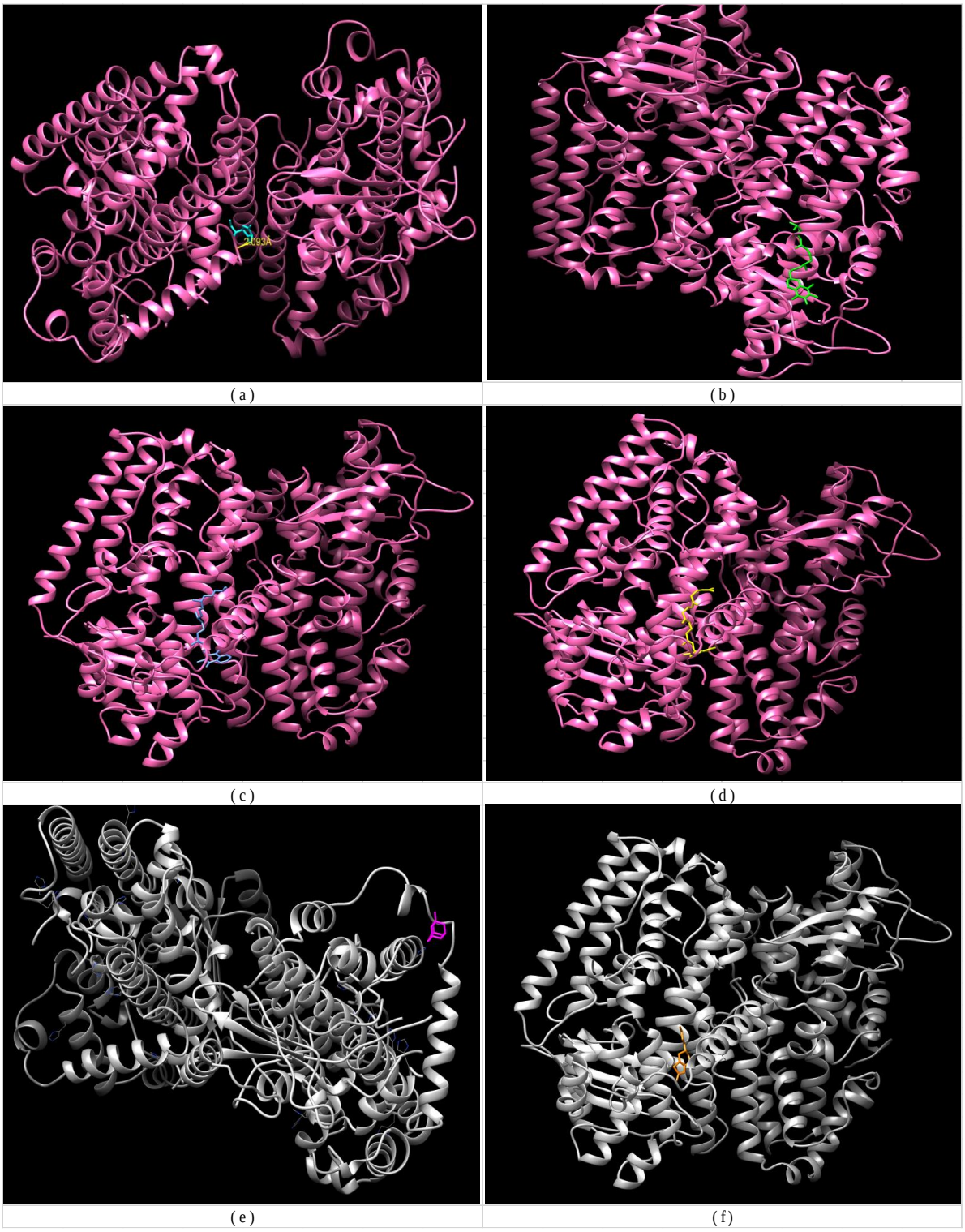


Figure 7: Docking Result of 12-Lipoxygenase with (a) Vitamin C, (b) Vitamin E, (c) Vitamin K1, (d) Vitamin K2, (e) Memantine, (f) Pramipexole

Protein	Ligand	E Value (kcal/mol)	ΔG Value (kcal/mol)	Full Fitness (kcal/mol)
12-Lipoxygenase	Vitamin C	-7.424	-7.932	-4231.155
	Vitamin E	-29.399	-9.032	-4274.577
	Vitamin K1	-30.241	-9.453	-4258.16
	Vitamin K2	-27.786	-9.143	-4231.143
	Memantine	-20.914	-6.697	-4262.505
	Pramipexole	-42.317	-6.995	-4300.617

Table 6: E Values of Vitamins and Controls

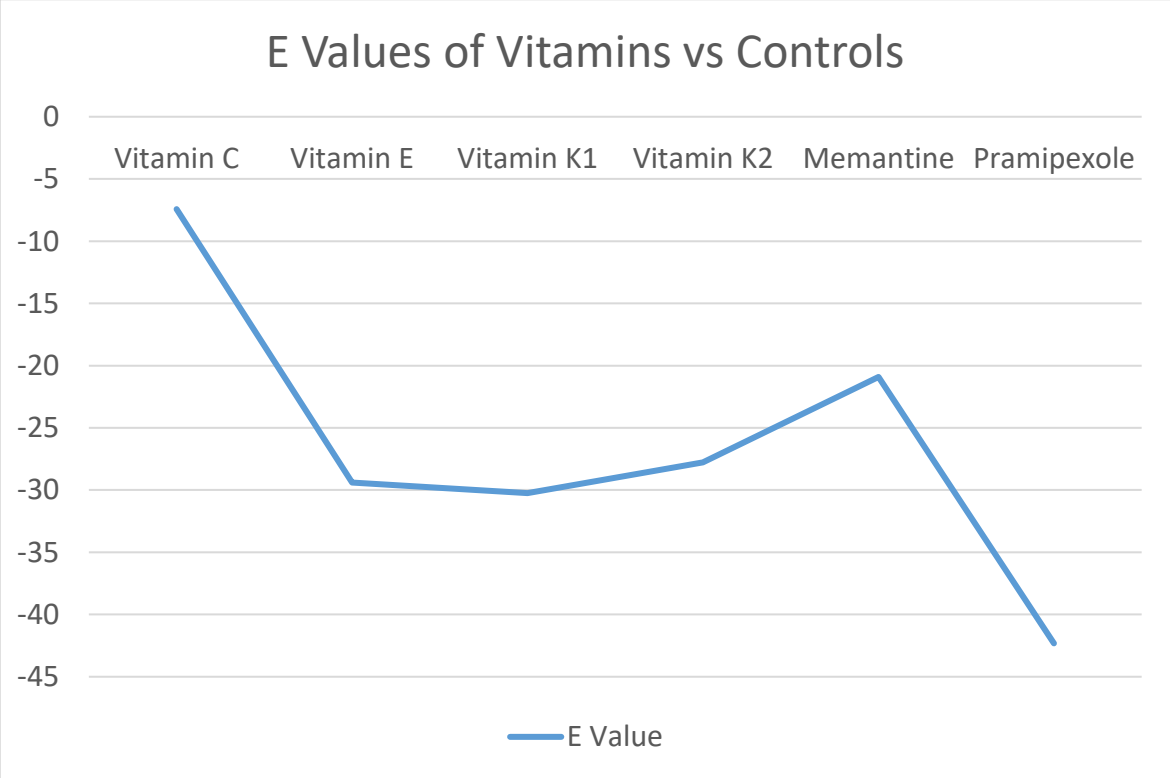


Figure 8: E Values of Vitamins vs Controls

Among the four vitamins studied, Vitamin K1 shows minimum E Value and therefore has the maximum affinity towards binding to 12-LOX, followed by Vitamin E, Vitamin K2 and Vitamin C respectively.

5. CONCLUSION AND DISCUSSION

Nowadays, computational drug designing has received so much importance in the industry as well as in research areas. It focusses on developing more reliable compounds against the biological target. In case of neurodegenerative disorders, the biggest challenge is the BBB permeability of the molecule. Several risk factors and side effects are always present. Therefore, an increased interest is observed in evaluating compounds of natural origin that can transverse BBB and can be used as potential molecules in neuroprotection. The role of dietary supplementation of vitamins has been previously suggested by various studies in reducing the risk of neurodegeneration. By structural activity relationship of vitamins, we suggest Vitamins as a potent therapeutic molecules in ameliorating the oxidative-stress mediated neurodegeneration.

There is, however, always some scope of advancement to attain more precise and accurate results. With respect to this study, the biggest challenge was selection of most related descriptors from thousands of computed parameters. Selection of all exactly related parameters is never assured which directly affects the accuracy of the results. But the aim is fulfilled since before actually testing the molecules as potential drugs, a brief idea of the predicted activity is accomplished so as to compare the calculated results to the computed ones. This also hints towards the idea that structurally similar compounds may behave similarly and possess similar biological activity. By actually analyzing the Structural Activity Relationships of different molecules and prediction of activities, selection of a better molecule for analysis is ensured which can further be utilized in Pharmacophore Modelling, QSAR Models, Drug Designing and even clinical studies.

As per our study Vitamin K1 shows the maximum potential towards inactivating the 12-LOX which is a mediator of production of free radicals through Arachidonic Acid Pathway. This gives a light of hope for further research that it may be used a substitute to the present drugs in ameliorating the oxidative injury caused by the oxidants and may open new doors to tackle the wrath of oxidative damage caused by free radicals by utilizing the molecules of natural origin.

6. REFERENCES

[1] J. M. S. Davies *et al.*, "The Oxygen Paradox, the French Paradox, and age-related diseases," *GeroScience*. 2017.

[2] A. Galano, R. Castañeda-Arriaga, A. Pérez-González, D. X. Tan, and R. J. Reiter, "Phenolic melatonin-related compounds: Their role as chemical protectors against oxidative stress," *Molecules*. 2016.

[3] J. J. Stephanos and A. W. Addison, "Valence Bond Theory and Orbital Hybridization," in *Electrons, Atoms, and Molecules in Inorganic Chemistry*, 2017.

[4] J. M. McCord, "Chapter 6 Mechanisms of cell injury by free radicals," *Princ. Med. Biol.*, 1998.

[5] M. Butnariu, "The Oxygen Paradox," *J. Pharmacogenomics Pharmacoproteomics*, 2012.

[6] D. Huang, O. U. Boxin, and R. L. Prior, "The chemistry behind antioxidant capacity assays," *Journal of Agricultural and Food Chemistry*. 2005.

[7] A. Kumar and R. R. Ratan, "Oxidative Stress and Huntington's Disease: The Good, the Bad, and the Ugly," *Journal of Huntington's Disease*. 2016.

[8] E. Niedzielska *et al.*, "Oxidative Stress in Neurodegenerative Diseases," *Molecular Neurobiology*. 2016.

[9] V. Dias, E. Junn, and M. M. Mouradian, "The role of oxidative stress in parkinson's disease," *Journal of Parkinson's Disease*. 2013.

[10] T. Masuda, M. Shimazawa, and H. Hara, "Retinal Diseases Associated with Oxidative Stress and the Effects of a Free Radical Scavenger (Edaravone)," *Oxid. Med. Cell. Longev.*, 2017.

[11] A. Dasgupta and K. Klein, "Oxidative Stress Related to Other Diseases," in *Antioxidants in Food, Vitamins and Supplements*, 2014.

[12] S. Salim, "Oxidative Stress and the Central Nervous System," *J. Pharmacol. Exp.*

Ther., 2016.

[13] S. B. Iloki-Assanga, L. M. Lewis-Luján, D. Fernández-Angulo, A. A. Gil-Salido, C. L. Lara-Espinoza, and J. L. Rubio-Pino, "Retino-protective effect of Bucida buceras against oxidative stress induced by H2O2 in human retinal pigment epithelial cells line," *BMC Complement. Altern. Med.*, 2015.

[14] I. M. Balmus, A. Ciobica, I. Antioch, R. Dobrin, and D. Timofte, "Oxidative Stress Implications in the Affective Disorders: Main Biomarkers, Animal Models Relevance, Genetic Perspectives, and Antioxidant Approaches," *Oxidative Medicine and Cellular Longevity*. 2016.

[15] E. Codorniu-Hernández, K. W. M. Hall, D. Ziemianowicz, S. Carpendale, and P. G. Kusalik, "Aqueous production of oxygen atoms from hydroxyl radicals," *Phys. Chem. Chem. Phys.*, 2014.

[16] J. A. Smith, S. Park, J. S. Krause, and N. L. Banik, "Oxidative stress, DNA damage, and the telomeric complex as therapeutic targets in acute neurodegeneration," *Neurochemistry International*. 2013.

[17] J. Li and Q. Pang, "Oxidative Stress-Associated Protein Tyrosine Kinases and Phosphatases in Fanconi Anemia," *Antioxid. Redox Signal.*, 2013.

[18] E. Tönnies and E. Trushina, "Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease," *Journal of Alzheimer's Disease*. 2017.

[19] S. Gandhi and A. Y. Abramov, "Mechanism of Oxidative Stress in Neurodegeneration," *Oxid. Med. Cell. Longev.*, 2012.

[20] G. H. Kim, J. E. Kim, S. J. Rhie, and S. Yoon, "The Role of Oxidative Stress in Neurodegenerative Diseases," *Exp. Neurobiol.*, 2015.

[21] Y. Gu, "Interaction of free radicals, matrix metalloproteinases and caveolin-1 impacts blood-brain barrier permeability," *Front. Biosci.*, 2011.

[22] T. Velusamy *et al.*, "Protective Effect of Antioxidants on Neuronal Dysfunction and Plasticity in Huntington's Disease," *Oxidative Medicine and Cellular Longevity*.

2017.

[23] X. Wang and E. K. Michaelis, “Selective neuronal vulnerability to oxidative stress in the brain,” *Frontiers in Aging Neuroscience*. 2010.

[24] C. A. Colton and D. L. Gilbert, “Production of superoxide anions by a CNS macrophage, the microglia,” *FEBS Lett.,* 1987.

[25] G. Cohen and R. E. Heikkila, “The generation of hydrogen peroxide, superoxide radical, and hydroxyl radical by 6 hydroxydopamine, dialuric acid, and related cytotoxic agents,” *J. Biol. Chem.,* 1974.

[26] B. Halliwell, “Oxidative stress and neurodegeneration: Where are we now?,” *Journal of Neurochemistry*. 2006.

[27] D. M. Miller, G. R. Buettner, and S. D. Aust, “Transition metals as catalysts of ‘autoxidation’ reactions,” *Free Radic. Biol. Med.,* 1990.

[28] X. Ren *et al.*, “Redox Signaling Mediated by Thioredoxin and Glutathione Systems in the Central Nervous System,” *Antioxid. Redox Signal.,* 2017.

[29] P. M. Sinet, R. E. Heikkila, and G. Cohen, “Hydrogen Peroxide Production by Rat Brain In Vivo,” *J. Neurochem.,* 1980.

[30] S. Wakatsuki, A. Furuno, M. Ohshima, and T. Araki, “Oxidative stress-dependent phosphorylation activates ZNRF1 to induce neuronal/axonal degeneration,” *J. Cell Biol.,* 2015.

[31] M. T. Lin and M. F. Beal, “Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases,” *Nature*. 2006.

[32] J. K. Andersen, “Oxidative stress in neurodegeneration: Cause or consequence?,” *Nat. Rev. Neurosci.,* 2004.

[33] E. Braak, K. Griffing, H. Bratzke, H. Braak, J. Bohl, and K. Arai, “Neuropathology of Alzheimer’s disease: what is new since A. Alzheimer?,” *Eur. Arch. Psychiatry Clin. Neurosci.,* 2006.

[34] G. S. Bloom, “Amyloid-β and tau: The trigger and bullet in Alzheimer disease pathogenesis,” *JAMA Neurol.*, 2014.

[35] Y. Stern, “Cognitive reserve in ageing and Alzheimer’s disease,” *The Lancet Neurology*. 2012.

[36] A. Federico, E. Cardaioli, P. Da Pozzo, P. Formichi, G. N. Gallus, and E. Radi, “Mitochondria, oxidative stress and neurodegeneration,” *J. Neurol. Sci.*, 2012.

[37] T. B. VanItallie, “Alzheimer’s disease: Innate immunity gone awry?,” *Metabolism.*, 2017.

[38] S.-Y. Kook, H. Seok Hong, M. Moon, and I. Mook-Jung, “Disruption of blood-brain barrier in Alzheimer disease pathogenesis,” *Tissue Barriers*, 2013.

[39] L. Mucke, “Neuroscience: Alzheimer’s disease,” *Nature*. 2009.

[40] B. T. Hyman, G. W. Van Hoesen, and A. R. Damasio, “Alzheimer’s disease: Glutamate depletion in the hippocampal perforant pathway zone,” *Ann. Neurol.*, 1987.

[41] D. M. Bowen and A. N. Davison, “Biochemical changes in the cholinergic system of the ageing brain and in senile dementia,” *Psychol. Med.*, 1980.

[42] D. G. Morgan, P. C. May, and C. E. Finch, “Dopamine and Serotonin Systems in Human and Rodent Brain: Effects of Age and Neurodegenerative Disease,” *J. Am. Geriatr. Soc.*, 1987.

[43] D. A. Loeffler *et al.*, “Transferrin and Iron in Normal, Alzheimer’s Disease, and Parkinson’s Disease Brain Regions,” *J. Neurochem.*, 1995.

[44] A. M. Palmer and M. A. Burns, “Selective increase in lipid peroxidation in the inferior temporal cortex in Alzheimer’s disease,” *Brain Res.*, 1994.

[45] D. L. Marcus *et al.*, “Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer’s disease,” *Exp. Neurol.*, 1998.

[46] A. Castegna, C. M. Lauderback, H. Mohmmad-Abdul, and D. A. Butterfield,

"Modulation of phospholipid asymmetry in synaptosomal membranes by the lipid peroxidation products, 4-hydroxynonenal and acrolein: Implications for Alzheimer's disease," *Brain Res.*, 2004.

[47] S. D. Yan *et al.*, "Glycated tau protein in Alzheimer disease: a mechanism for induction of oxidant stress.," *Proc. Natl. Acad. Sci. U. S. A.*, 1994.

[48] M. A. Smith, P. L. Richey Harris, L. M. Sayre, J. S. Beckman, and G. Perry, "Widespread peroxynitrite-mediated damage in Alzheimer's disease.," *J. Neurosci.*, 1997.

[49] M. A. Pappolla, R. A. Omar, K. S. Kim, and N. K. Robakis, "Immunohistochemical evidence of oxidative [corrected] stress in Alzheimer's disease.," *Am. J. Pathol.*, 1992.

[50] C. Behl, J. Davis, G. M. Cole, and D. Schubert, "Vitamin E protects nerve cells from amyloid βprotein toxicity," *Biochem. Biophys. Res. Commun.*, 1992.

[51] C. Behl, J. B. Davis, R. Lesley, and D. Schubert, "Hydrogen peroxide mediates amyloid β protein toxicity," *Cell*, 1994.

[52] F. Coppedè and L. Migliore, "DNA damage in neurodegenerative diseases," *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis*. 2015.

[53] X. Shan and C. liang G. Lin, "Quantification of oxidized RNAs in Alzheimer's disease," *Neurobiol. Aging*, 2006.

[54] U. Ungerstedt, "Adipsia and Aphagia after 6-Hydroxydopamine Induced Degeneration of the Nigro-striatal Dopamine System," *Acta Physiol. Scand.*, 1971.

[55] M. C. Rodriguez-Oroz *et al.*, "Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms," *The Lancet Neurology*. 2009.

[56] T. G. Hastings, "The role of dopamine oxidation in mitochondrial dysfunction: Implications for Parkinson's disease," *Journal of Bioenergetics and Biomembranes*. 2009.

[57] L. Zecca *et al.*, “Human neuromelanin induces neuroinflammation and neurodegeneration in the rat substantia nigra: Implications for Parkinson’s disease,” *Acta Neuropathol.*, 2008.

[58] P. Jenner and J. W. Langston, “Explaining ADAGIO: A critical review of the biological basis for the clinical effects of rasagiline,” *Movement Disorders*. 2011.

[59] J. Saura, N. Andrés, C. Andrade, J. Ojuel, K. Eriksson, and N. Mahy, “Biphasic and region-specific MAO-B response to aging in normal human brain,” *Neurobiol. Aging*, 1997.

[60] M. B. H. Youdim, D. Edmondson, and K. F. Tipton, “The therapeutic potential of monoamine oxidase inhibitors,” *Nature Reviews Neuroscience*. 2006.

[61] T. Nagatsu and M. Sawada, “Molecular mechanism of the relation of monoamine oxidase B and its inhibitors to Parkinson’s disease: possible implications of glial cells,” in *Oxidative Stress and Neuroprotection*, 2006.

[62] M. J. Kumar and J. K. Andersen, “Perspectives on MAO-B in Aging and Neurological Disease: Where Do We Go From Here?,” *Mol. Neurobiol.*, 2004.

[63] R. K. B. Pearce, A. Owen, S. Daniel, P. Jenner, and C. D. Marsden, “Alterations in the distribution of glutathione in the substantia nigra in Parkinson’s disease,” *J. Neural Transm.*, 1997.

[64] M. Hsu *et al.*, “Inducible Alterations of Glutathione Levels in Adult Dopaminergic Midbrain Neurons Result in Nigrostriatal Degeneration,” *J. Neurosci.*, 2007.

[65] M. Garrido, Y. Tereshchenko, Z. Zhevtsova, G. Taschenberger, M. Bähr, and S. Kügler, “Glutathione depletion and overproduction both initiate degeneration of nigral dopaminergic neurons,” *Acta Neuropathol.*, 2011.

[66] D. J. Surmeier, J. N. Guzman, J. Sanchez-Padilla, and P. T. Schumacker, “The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in Parkinson’s disease,” *Neuroscience*. 2011.

[67] R. J. Miller *et al.*, “Calcium Entry and -Synuclein Inclusions Elevate Dendritic

Mitochondrial Oxidant Stress in Dopaminergic Neurons," *J. Neurosci.*, 2013.

[68] E. V. Mosharov *et al.*, "Interplay between Cytosolic Dopamine, Calcium, and α-Synuclein Causes Selective Death of Substantia Nigra Neurons," *Neuron*, 2009.

[69] S. E. Browne, R. J. Ferrante, and M. F. Beal, "Oxidative Stress in Huntington's Disease," *Brain Pathol.*, 2010.

[70] S. E. Browne, R. J. Ferrante, and M. F. Beal, "Oxidative stress in Huntington's disease [In Process Citation]," *Brain Pathol*, 1999.

[71] S. E. Browne and M. F. Beal, "Oxidative Damage in Huntington's Disease Pathogenesis," *Antioxid. Redox Signal.*, 2006.

[72] S. E. Browne *et al.*, "Oxidative damage and metabolic dysfunction in huntington's disease: Selective vulnerability of the basal ganglia," *Ann. Neurol.*, 1997.

[73] S. E. Browne, R. J. Ferrante, and M. F. Beal, "Oxidative stress in Huntington's disease.," *Brain Pathol.*, 1999.

[74] H. BRAAK and E. BRAAK, "Allocortical involvement in Huntington's disease," *Neuropathol. Appl. Neurobiol.*, 1992.

[75] F. Walker, "Huntington's disease. [Lancet. 2007] - PubMed - NCBI," *Lancet*, 2007.

[76] B. Halliwell and J. M. C. Gutteridge, "Gutteridge Free Radicals in Biology and Medicine," *Oxford University Press. 888 pp.* 2007.

[77] R. Kohen, E. Beit-Yannai, E. M. Berry, and O. Tirosh, "Overall low molecular weight antioxidant activity of biological fluids and tissues by cyclic voltammetry," *Methods Enzymol.*, 1998.

[78] B. Halliwell, "Free radicals, antioxidants, and human disease: curiosity, cause, or consequence?," *Lancet*, 1994.

[79] T. Siddique, H. X. Deng, and S. Ajroud-Driss, "Chapter 132 – Motor Neuron Disease," in *Emery and Rimoin's Principles and Practice of Medical Genetics*, 2013.

[80] K. Dasuri, L. Zhang, and J. N. Keller, “Oxidative stress, neurodegeneration, and the balance of protein degradation and protein synthesis,” *Free Radical Biology and Medicine*. 2013.

[81] C. M. Maier and P. H. Chan, “Role of superoxide dismutases in oxidative damage and neurodegenerative disorders,” *Neuroscientist*. 2002.

[82] M. V Fanucchi, “Chapter 11 - Development of Antioxidant and Xenobiotic Metabolizing Enzyme Systems,” in *The {Lung} ({Second} {Edition})*, 2014.

[83] R. Brigelius-Flohé and M. Maiorino, “Review: Glutathione peroxidases,” *Biochim Biophys Acta*, 2013.

[84] J. H. T. Power and P. C. Blumbergs, “Cellular glutathione peroxidase in human brain: Cellular distribution, and its potential role in the degradation of Lewy bodies in Parkinson’s disease and dementia with Lewy bodies,” *Acta Neuropathol.*, 2009.

[85] M. Naziroğlu, “Molecular role of catalase on oxidative stress-induced Ca2 signaling and TRP cation channel activation in nervous system,” *Journal of Receptors and Signal Transduction*. 2012.

[86] A. Perkins, K. J. Nelson, D. Parsonage, L. B. Poole, and P. A. Karplus, “Peroxiredoxins: Guardians against oxidative stress and modulators of peroxide signaling,” *Trends in Biochemical Sciences*. 2015.

[87] C. Espinosa-Diez *et al.*, “Antioxidant responses and cellular adjustments to oxidative stress,” *Redox Biology*. 2015.

[88] T. D. Oberley, E. Verwiebe, W. Zhong, S. W. Kang, and S. G. Rhee, “Localization of the thioredoxin system in normal rat kidney,” *Free Radic. Biol. Med.*, 2001.

[89] M. S. Seo, S. W. Kang, K. Kim, I. C. Baines, T. H. Lee, and S. G. Rhee, “Identification of a new type of mammalian peroxiredoxin that forms an intramolecular disulfide as a reaction intermediate,” *J. Biol. Chem.*, 2000.

[90] K. Krapfenbauer, E. Engidawork, N. Cairns, M. Fountoulakis, and G. Lubec, “Aberrant expression of peroxiredoxin subtypes in neurodegenerative disorders,”

Brain Res., 2003.

[91] H. J. Forman, H. Zhang, and A. Rinna, "Glutathione: Overview of its protective roles, measurement, and biosynthesis," *Molecular Aspects of Medicine*. 2009.

[92] J. E. Pizzorno and J. J. Katzinger, "Glutathione: Physiological and Clinical Relevance," *J. Restor. Med.*, 2013.

[93] C. Mytilineou, B. C. Kramer, and J. A. Yabut, "Glutathione depletion and oxidative stress," *Parkinsonism and Related Disorders*. 2002.

[94] E. Beutler, "Disorders Due to Enzyme Defects in the Red Blood Cell," 2013.

[95] S. N. Savvides *et al.*, "Crystal structure of the antioxidant enzyme glutathione reductase inactivated by peroxynitrite," *J. Biol. Chem.*, 2002.

[96] J. Kocot, D. Luchowska-Kocot, M. Kiełczykowska, I. Musik, and J. Kurzepa, "Does vitamin c influence neurodegenerative diseases and psychiatric disorders?," *Nutrients*. 2017.

[97] N. Crouzin, M. C. de Jesus Ferreira, C. Cohen-Solal, G. Barbanel, J. Guiramand, and M. Vignes, "Neuroprotection induced by vitamin e against oxidative stress in hippocampal neurons: Involvement of TRPV1 channels," *Mol. Nutr. Food Res.*, 2010.

[98] İ. Gülçin, "Antioxidant Activity of Eugenol: A Structure–Activity Relationship Study," *J. Med. Food*, 2011.

[99] G. Ruberto and M. T. Baratta, "Antioxidant activity of selected essential oil components in two lipid model systems," *Food Chem.*, 2000.

[100] J. D. McKinney, "The Practice of Structure Activity Relationships (SAR) in Toxicology," *Toxicol. Sci.*, 2000.

[101] H. Cao, W. X. Cheng, C. Li, X. L. Pan, X. G. Xie, and T. H. Li, "DFT study on the antioxidant activity of rosmarinic acid," *J. Mol. Struct. THEOCHEM*, 2005.

[102] J. A. Padrón, R. Carrasco, and R. F. Pellón, "Molecular descriptor based on a molar

refractivity partition using Randictype graph-theoretical invariant," *J. Pharm. Pharm. Sci.*, 2002.

[103] A. H. Pandith, S. Giri, and P. K. Chattaraj, " A Comparative Study of Two Quantum Chemical Descriptors in Predicting Toxicity of Aliphatic Compounds towards Tetrahymena pyriformis ," *Org. Chem. Int.*, 2011.

[104] J. I. Aihara, "Reduced HOMO-LUMO Gap as an Index of Kinetic Stability for Polycyclic Aromatic Hydrocarbons," *J. Phys. Chem. A*, 1999.

[105] A. Mauri, V. Consonni, M. Pavan, and R. Todeschini, "DRAGON software: an easy approach to molecular descriptor," *Commun. Math. Comput. Chem.*, 2006.

[106] F. Furche, R. Ahlrichs, C. Hättig, W. Klopper, M. Sierka, and F. Weigend, "Turbomole," *Wiley Interdiscip. Rev. Comput. Mol. Sci.*, 2014.

[107] G. Kahl, "MOPAC," in *The Dictionary of Genomics, Transcriptomics and Proteomics*, 2015.

[108] H. Liu *et al.*, "AlzPlatform: An Alzheimer's disease domain-specific chemogenomics knowledgebase for polypharmacology and target identification research," *J. Chem. Inf. Model.*, 2014.

[109] A. Lagunin, A. Stepanchikova, D. Filimonov, and V. Poroikov, "PASS: Prediction of activity spectra for biologically active substances," *Bioinformatics*, 2000.

[110] H. M. Berman *et al.*, "The Protein Data Bank Helen," *Nucleic Acids Res.*, 2000.

[111] A. Gupta, A. Gandhimathi, P. Sharma, and B. Jayaram, "ParDOCK: an all atom energy based Monte Carlo docking protocol for protein-ligand complexes.," *Protein Pept. Lett.*, 2007.

[112] A. Grosdidier, V. Zoete, and O. Michielin, "SwissDock, a protein-small molecule docking web service based on EADock DSS," *Nucleic Acids Res.*, 2011.