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IN-SILICO MOLECULAR DOCKING AND PHARMACOKINETIC STUDIES OF SOME SELECTED PHYTO-CONSTITUENTS OF BRYOPHYLLUM PINNATUM AS A POTENTIAL SELECTIVE INHIBITOR OF MONOAMINE OXIDASE–B (MAO-B)

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Abstract

Monoamine oxidase (EC, 1.4.3.4) is an important biological enzyme that catalyzes the oxidation of monoamines. It is critical for the inactivation of neurotransmitters. Monoamine oxidase (MAO) exists in two isoforms; A and B. Abnormality in the activity of the monoamine oxidase B has been associated with neurological dysfunctions such as Alzheimer's disease. An insight into the interaction of monoamine oxidase B binding site with inhibitors is crucial for the development of new pharmaceutical agents. In this study, we examined the inhibitory activity of human MAO-B and a series of bioactive ligands from *Bryophyllum pinnatum* as potential Monoamine oxidase B inhibitors. Computational docking analysis was performed using extra precision (XP) feature of Glide module, version 5.6. The final products of molecular docking were clustered to specify the binding free energy and Kinetic inhibition (Ki) was calculated. Docking results showed all the compounds tested (patuletin, luteolin, kaempferol and acacetin) had high binding score compared to the standard reference drugs. Specifically, patuletin, an O-methylated flavonol had the optimum binding affinity (-10.105kcal/Mol) compared to the standard drugs selegiline (–7.82 kcal/mol) and rasagiline (-7.82). Hydrogen bond interactions between the 3-OH of patuletin and Tyr-435 and Ile-199 of the active residues were found to have played a critical role in stabilizing the ligand bond at the active site. This present study provides salient information for the rational drug design of more potent and selective Monoamine oxidase B inhibitors in the management of neuro-degenerative disorders. Further *in-vitro* and *in-vivo* studies validating the inhibitory activity of Patuletin is highly recommended.

Keywords: *Monoamine Oxidase Inhibitor B (MAO-B), Molecular Docking, Neuro- degeneration, Phyto-constituents, Patuletin*

Introduction

The human monoamine oxidase (MAO) is a flavin-adenine-dinucleotide (FAD)-containing enzyme localized in the outer mitochondrial membranes of the brain, liver, intestinal mucosa and other organs [1,2,3]. MAO plays a significant physiological role in the central nervous system and peripheral organs. It also catalyses the oxidative deamination of biogenic amines (neurotransmitters, vasoactive and xenobiotic amines), including dopamine, serotonin, nor-ephinephrine, tyramine, tryptamine and (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) MPTP neurotoxin [4]. The oxidation of biogenic amines by MAO results in the production of hydrogen peroxide and aldehydes which may represent a risk factor for cell oxidative injury [5]. MAO exists in two isoforms; MAO-A and MAO-B, encoded by two distinct gene loci, distributed in varying patterns in the tissue [1] and distinguished by their differences in substrate and inhibitor selectivity.

MAO-A preferentially oxidizes serotonin and norepinephrine and is sensitive to selective inhibitors while MAO-B isoform preferentially oxidizes phenylethylamine and is selectively inhibited by inhibitors such as selegline. About 80% of the total MAO activity in the human brain is reported to be MAO-B [6]. Abnormal activity of MAO-B has been implicated in neurological disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD). Previous studies have reported increased activities of MAO-B in the brain and blood platelets of patients suffering from neurodegenerative diseases [7]. The increase in brain MAO-B concentration is believed to be attributed to transcriptional elevation of MAO-B protein in the brain [8]. However, the reason leading to an increase in platelet MAO-B activity is still unknown. Inhibitors of MAO-B block the activity of MAO-B leading to enhanced dopaminergic neurotransmission and prevent activation of toxin and free radical formation as well as alleviate the process of neuron denaturalization [9]. Studies have shown that the inhibitors (what type of inhibitors?) of MAO-B have been linked with an increased risk of associated side effects once taken with some specific diets [10]. Hence, there is a need to identify new potent selective MAO-B inhibitors for the management of MAO-B associated neuro-degenerative diseases.

Molecular docking has become an indispensable tool to the pharmaceutical industry and academia over the last decade [11]. It has been employed during various stages of the pre-clinical drug design process. Rational drug design using computational biology and bioinformatics have the potential not only to speed up the drug discovery process, but also reduce cost and improve the way drugs are designed.

Nature remains an ever-evolving source for small molecules in medicine. Natural compounds derived from medicinal plants for the treatment of ailments are well known and documented since pre-historic times. Communities of Sub Saharan Africa have depended on natural medicine to solve various health challenges from simple to complex situations [12]. In recent times, there has been a renewed interest in developing novel lead molecules from plant sources because of their higher biological activity, safety and lower cost as compared to the synthetic drugs [13]. Although, a lot of research has been carried out on the chemical characterization of phytochemicals, antioxidant properties and anti-aging potential of some tropical Nigerian medicinal plants, there is still limited information on their inhibitory effect on Monoamine Oxidase B.

Bryophyllum pinnatum is a succulent perennial herb belonging to the family of Crassulaceae. It is grown in tropical Africa, India, China, Australia and tropical America. *B. pinnatum* is widely distributed in Southern Nigeria and has been extensively researched for its use in the treatment of ailments [14]. Recent studies on the isolation and characterization of *B. Pinnatum* have shown the presence flavonoids [15, 16]. Other bioactive compounds found to be present include glycosides, steroids, bufadienolides, alkaloids, triterpenes, cardienolides, steroids, and organic acids [17, 18]. In traditional medicine, the plant has been reportedly used for the treatment of many aliments such as hypertension, cough, diabetes mellitus, bruises, wounds, boils, abscesses, insect bites, arthritis, rheumatism, joint pains, childbirth, headaches and body pains [17, 19]. Therefore, the phyto-constituents of *B. Pinnatium* identified could act as a good source of therapeutic agents. Hence, this study seeks to identify from *B. pinnatium* novel inhibitors of MAO-B in neuro-degeneration *in-silico*.

Methods

Preparation of Macro-molecule

The 3-Dimensional crystal structure of MAO-B (Figure 1) in complex with rosiglitazone (PDB: 4A7A) with crystallographic resolution of 1.7Å was downloaded from the RCSB Protein Data Bank (http://www.rcsb.org). The missing residues and atoms were restored using the protein preparation wizard on Schrodinger.

Preparation of Phyto- Ligand

Phyto-ligands used for this study were selected based on the chemical characterization of *B. pinnatum* plants previously reported in literature [15, 16, 18]. The 2D SDF structures of the selected phyto-ligands (Figure 2) were retrieved from PubChem Database (https://pubchem.ncbi.nlm.nih.gov). The structures were downloaded in SDF format and were then converted to PDB format using Open babel 2.1.2.

Molecular Docking Analysis

Molecular Docking was performed using the extra precision (XP) feature of Glide module, version 5.6 [21]. The constraints to define ligand-receptor interactions were not set. The structure output format was set to pose viewer file so as to view the output of the resulting docking studies from pose viewer. Only the coordinates of chain B and FAD were considered as the receptor structure. The co-crystallized inhibitor and water molecules were removed for the docking studies. Receptor grid coordinates were generated using 60 × 60 × 60 grid points in xyz with grid spacing of 0.375 Å. (X= 21.970, Y=128.899, Z=16.057). During the docking procedure, both the protein and ligands were considered as rigid. The results less than 1.0 Å in positional root-mean-square deviation (RMSD) were clustered together and represented by the result with the most favourable free energy of binding. The pose with lowest binding energy was extracted and aligned with receptor structure for further analysis.

Validation of docking results

The docking results were validated with the blasting of the fasta sequences of the crystal structure of the ligand-binding domain of the human MAO-B (ID: 4A7A), obtained from the protein data bank unto the online available ChEMBL Database (www.ebi.ac.uk/chembl/). The bioactivity generated by the database, having an identity of 100%, IC50 value of 3051, and Ki value of 476, was downloaded in txt format. The bioactivity was sorted out; missing or misplaced data were removed. Only 88 of the total 2599 drug-like compounds were recovered. The compiled compounds were split and converted to 2D (in sdf format) by Data Warrior software (version 2), converted to pdb format by Open Babel, and finally to pdbqt. The ligands were docked into the binding domain of MAO-B (as indicated by the config file). The config file indicated the grid map of the active site of MAO-B generated using the extra precision (XP) feature of Glide module, version 5.6. Correlation coefficient graph was plotted between the docking scores of the 80 compounds generated and their corresponding pIC50 (experimentally determined) values. Spearman Rank correlation co-efficient graph was plotted to obtain the correlation (R^2) between the dockings results of the ChEMBL's compounds and their corresponding experimentally generated results.

Drug Likeness Prediction

In-silco prediction of molecular descriptors and drug likeness properties of phyto- ligands was estimated using the tool Molinspiration server (http://www.molinspiration.com) [23]. MW (molecular weight), LogP, HBD (number of hydrogen bond donors), HBA (number of hydrogen bond acceptors), TPSA (topological polar surface area), nrtB (number of Rotatable bonds), nViolation (violations of Lipinski's rule of five) were calculated on the basis of Lipinski rule of five [24].

ADME prediction Studies

Prediction of ADMET properties was carried out using admetSAR prediction online tool (http://lmmd.ecust.edu.cn:8000/) or (http://www.admetexp.org) database. The ADMET properties of a compound show the absorption, distribution, metabolism, excretion, and toxicity in and through the human body. This elucidates the pharmacokinetic profile of a drug molecule which is vital in evaluating its pharmacodynamics activities. Today, various online tools and offline software programs are available which provides insight in predicting this behaviour of the drug candidate.

Results and Discussion

Glide docking tool was employed to describe and determine the binding sites in monoamine oxidase B. The best docked structure was clustered to specify the binding free energy and optimal docking energy conformation. The docking results indicate that all compounds were bound to monoamine oxidase B active site which consists of a hydrophobic pocket surrounded by the aromatic and aliphatic residues. The active site of monoamine oxidase B is made up of a dipartite cavity structure, consisting of an entrance and substrate cavity separated by two side chain Ile 199 and Tyr 329 that becomes fused upon binding of an inhibitor [25, 26]. The crystal structure of the enzyme inhibitor complex shows that the R-enantiomer is bound with thiazolidinedione ring near the Flavin moiety. The molecule occupies both substrate and entrance cavities which is similar to the orientation of our docked compounds.

Binding Energies

In this study, main interactions of some phyto-constituents of leaves *of B. Pinnatium* [17,18] with the main residues at the active site (Tyr 60, Tyr 326, Tyr435, Cys 172, Ile 198, Leu 171, Gln 206) were observed. Table 1 summarizes the binding energies and kinetic inhibition. The results of the binding score were represented in negative value indicating that the compounds were correctly docked into the crystal structure of MAO-B. As shown in (Table 1), all compounds docked showed good binding energies ranging from -4.062kcal/mol – 10.105 Kcal/mol. We validated the accuracy of our docking protocol by superimposing the co-crystallized ligand rosiglitazone back into the binding pocket of the MAO-B (4A7A), (Figure 3). As shown in figure 3, the re-docked pose overlapped almost totally with the experimental orientation of MAO-B, this implies that our docking methodology is reliable and the docking scores obtained are correct. Patuletin, kaempferol, luteolin and acacetin had the best scores with the lowest binding free energy of (-10.105 kcal/mol,-8.467kcal/mol, -8.453kcal/mol and 7.890kcal/mol) respectively compared to the synthetic MAO-B inhibitors rasagiline and selegiline (-4.062kcal/mol, 7.284, -7.865kcal/mol). Ordinarily, a greater or more potent interaction bears a direct relationship with more negative free binding energy.

The accuracy of our docking scores was further validated using the online available ChEMBL Database, the Fasta sequence of the crystal structure of the Human MAO-B (ID: 4A7A) was blasted on www.ebi.ac.uk/chembl/. The strong correlation coefficient of 0.721 was observed between the docking scores and the experimentally derived data in the present study, lending credence to the fact that computational experiment can replicate experimental data at least in this present study and that our docking scores using extra precision (XP) feature of Glide module, is dependable (Figure 4).
In molecular docking, the known or predicted shape of the binding site is used to optimize the ligand as a best fit to the receptor. The orientations of these ligands play a significant role in interaction between active site residues [28] Figure 5 (i-vii) shows that the binding manner and geometrical orientation of all compounds in the active site were nearly identical, hence proposing that all the inhibitors have similar interactions with MAO-B and occupied a common space in the binding pocket of the receptor. Phyto-ligands with the highest binding energies were highlighted further to study their interactions. Figure 5 i-vii shows a visual observation of the docked conformation of patuletin (5i), luteolin (5ii) kaempferol (5iii) and their synthetic counterparts to MAO-B active site, indicating interactions with the main residues at the active site. *Patuletin* was fused inside the substrate cavity caged by Tyr435, Tyr398, Phe168, Cys172, Leu171, Phe343, Ile199, Tyr326, Ile 198, Tyr 326 amino acid residues (Figure 5i). Furthermore, luteolin, kaempferol, two synthetic ligands and the co-ligand were shown to have similar amino acid residues observed within the 4A radius of the active site when bound MAO-B. Weak molecular interaction such as hydrophobic and hydrogen bonds are generally considered good facilitators of protein-ligand binding [29]. They contribute specifically to the efficacy and stability of a ligand at the active site of a protein structure [28]. In this study, we explored the weak intermolecular interactions on the ligand-protein complexes with high binding affinity. Specifically, pateultin also known as 6-methoxyquercetin or quercetagetin 6-methyl ether, is a member of the class of compounds known as flavonols. Flavonols are compounds that contain a flavone (2-phenyl-1-benzopyran-4-one) backbone carrying a hydroxyl group at the 3-position. (Figure 6(i) show hydrogen bond interactions with OH and Tyr 435 and Ile 199. Furthermore,luteolin, kaempferol

and acacetin (Figure 6(ii- iv) demonstrated similar hydrogen bond interaction indicating that these interactions are important to explain the biological activity of the MAO-B inhibitors.

Drug-likeness Prediction

For any molecule to be considered as a drug, it has to obey Lipinski's rule of five [24], which stipulates that poor absorption or permeation is more likely when there are < 5 H-bond donors, molecular weight < 500 g/mol, the Log P (cLog P) < 5, and there are < 10 H-bond acceptors. Designing drugs for the human brain requires optimal penetration and optimal concentration at the desired therapeutic target. This is a major challenge in the central nervous system (CNS) drug discovery pipeline, due to the complex protective system of the brain [30]. For any compound to be considered as a lead CNS drug candidate, certain physiochemical criteria must be met. Penetration of the blood-brain barrier is a major physicochemical feature that a CNS drug requires to exhibit CNS activity [31]. CNS drugs tend to possess lower values of molecular weight< 450, lipophilicity, hydrogen bond donor and acceptor compared to general non- CNS drugs.

In this study, patuletin, luteolin, kaempferol and acacetin passed the Lipinski rule of five as shown in Table 3. The polar surface area (PSA) and the molecular volume components are the most important descriptors for brain barrier permeability described as the surface area ($Å^2$) occupied by nitrogen and oxygen atoms and the polar hydrogens attached to them and is strongly reflective of hydrogen bonding capacity and polarity [32]. Feng [33] reported that compounds aimed at the CNS tend to have lower PSA values < 90 $Å^2$compared to other classes of therapeutic drugs which is< 140 $Å^2$. The findings of this study show that patuletin, luteolin and Kaempferol having good binding scores showed a TPSA of > 90 $Å^2$. This could indicate poor BBB CNS permeability even while showing considerable drug likeness. However, acacetin had a good TPSA value of 79$Å^2$ indicating good BBB permeability.

ClogP is said to correlate proportionately with blood brain barrier (BBB) penetration, hence increasing lipophilicity with increasing brain penetration [34]. Blood-brain barrier penetration is optimal when the CLogP values are in the range of 1.5-2.7, with the mean value of 2.1 suggesting that compounds within the range are potent for brain and intestinal permeability [34]. Table 3 indicate that all the compounds had log p values within the normal range.

ADMET prediction results of some compounds of B. pinnatum

Absorption, distribution, metabolism, excretion and toxicity properties of phyto-ligands were investigated using admetSAR [35]. Human Intestinal Absorption (HIA), Caco- 2 cell permeability, Blood-Brain Barrier (BBB) penetration, and Ames test were calculated. The predicted ADMET data are summarized in Table 4. The results showed that all test compounds could be absorbed by the human intestine, although, luteolin and kaempferol showed poor Caco-2 cell permeability Table 4. P-glycoprotein (P-gp) is a trans-membrane efflux pump which removes drugs from the cell membrane and cytoplasm causes compounds to undergo further metabolism and clearance [36] resulting in therapeutic failure because the drug concentration would be lower than expected [37]. The study showed patuletin to be a substrate for P-glycoprotein, responsible for drug effluxes and various compounds to undergo further metabolism and clearance. Hence, dosage control and knowledge of co-administered drugs might be considered to reduce therapeutic failure. Based on the predicted values of admetSAR, all the selected phyto-ligands can be absorbed by human intestines. Cytochrome P450 are a super family of metabolising enzymes that play an important role in drug metabolism and clearance in the liver, and the most important isoforms are CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4[38]. Thus, inhibition of cytochrome P450 isoforms might cause drug-drug interactions in which co-administered drugs fail to metabolized and accumulate to toxic levels [39, 40]. Notwithstanding, some of the cytochrome P450 isoforms were found to have inhibited by one or more of the tested compounds. Furthermore, all the compounds did not show any acute toxicity and mutagenic effect with respect to the AMES test data.

Conclusion

This current study has shown the binding interaction and pharmacokinetics of flavonoid rich

phyto constituent of *B. pinnatum* to the MAO-B enzyme would enable the design of new MAO-B inhibitors. The binding models of the inhibitors demonstrated how these compounds bind to MAO-B enzyme. The binding free energies of these compounds to MAO-B were found to have a good correlation with other experimental inhibitory activities. The most favourable binding mode of patuletin top-ranking compounds might be useful in designing new MAO-B inhibitors for the treatment of neuro-degenerative diseases. Further studies are required to validate the potential efficacy of the plant and compounds using cellular and animal models.

Conflict of interest

The authors declare no conflict of interest.

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Table 1: Showing the binding energies of some compounds of ***B. pinnatum*** with MAO-B

S/N	Compound Name	Chemical Formula	Binding energies (Kcal/mol)
	Patuletin	$C_{16}H_{12}O_8$	-10.105
	Luteolin	$C_{15}H_{10}O_6$	-8.467
	Kaempferol	$C_{15}H_{10}O_6$	-8.452
	Acacetin	$C_{16}H_{12}O_5$	-7.890
	Selegiline	$C_{13}H_{17}N$	-7.865
	Coligand	$C_{18}\ H_{19}\ N_3\ O_3\ S$	-7.0

Table 2: Showing the side chains within 4A radius of MAO-B

1.	Patuletin	TYR435, TYR398, PHE168, CYS172, LEU171, PHE343,ILE199,TYR326, ILE 198, TYR 326
2.	Luteolin	LEU 164, PRO102,PRO 104, GLN 206, TYR 326, TYR 435, CYS172, ILE198, GLN206,
3.	Kaempferol	TYR435, TYR396, GLN206, CYS172, PRO102, TYR326, PRO104, ILE199, PHE168, ILE198
4.	Acacetin	PHE343, LYS296, TYR60, TYR435, GLY434, LEU171, ILE198, CYS172, TRY398
5.	Selegiline	PHE343, CYS172, GLN206, TYR 435, TYR 398, TYR 326, LEU 171, LEU164, PRO104
6.	Rasagiline	GLY57, TYR434, TYR398, VAL384, LEU171, LYS291, PHE343,TYR60

Table 3: Drug-likeness Prediction results of some compounds of *B. pinnatium* based on Linpinski rule of 5

S/N	Compound Name	MW g/mol	NOR	HBA	HBD	Xlog P	TPSA (Å²)	NOV
1.	Patuletin	332.26	2	8	5	1.70	140.5	0
2.	Luteolin	286.24	1	6	4	1.97	111.12	0
3.	Kamepferol	286.24	1	6	4	2.17	111.12	0
4.	Acacetin	284.26	2	5	2	3.00	79.9	0
6.	Selegiline	187.28	4	1	0	2.64	3.2	0
5.	Rasagiline	171.24	2	1	1	2.1	12.0	0

MW: Molecular weight (<500), NOR: Number of Rotable Atoms, HBA: Number of Hydrogen Bond Acceptors (<10), HBD: Number of Hydrogen Bond Donor (<5), XlogP ≤ 5, TPSA: Topological Polar Surface Area, NOV: Number of Violation of Lipinski's rule.

Table 4: ADME prediction results of some compounds of *B. Pinnatum*

Compound	HIA	Caco-2 Permeability	BBB	p-gp Substrate / Inhibition /	CYP Inhibition/ Substrate	AMES/ toxicity	Carcinogenicity	LD_{50} in rats
Patuletin	HIA+	Caco2+	BBB-	Substrate /non inhibitor	Non-substrate/inhibitor	Non-toxic	Non-carcinogen	2.6388
Luteolin	HIA+	Caco2-	BBB-	Substrate /non inhibitor	Non-substrate / inhibitor	Non-toxic	Non-carcinogen	3.0200
Kaempferol	HIA+	Caco2-	BBB+	Substrate /non inhibitor	Non–substrate /inhibitor	Non-toxic	Non-carcinogen	3.0825
Acacetin	HIA+	Caco2+	BBB-	Substrate /non inhibitor	substrate/inhibitor	Non-toxic	Non-carcinogenic	2.445
Rasagiline	HIA+	Caco2+	BBB+	Non-substrate/ Non inhibitor	Substrate / inhibitor	Non – toxic	Non-carcinogenic	2.8164
Selegiline	HIA+	Caco2+	BBB+	Non-substrate / Non inhibitor	Non substrate /Non inhibitor	Non-toxic	Non carcinogenic	2.9199

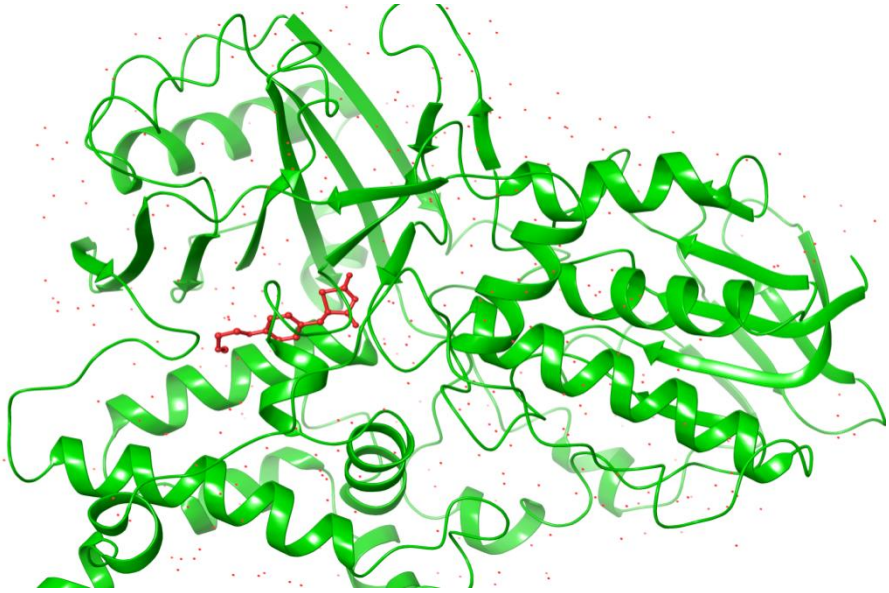


Figure. 1: 3Dimenstional Crystal structure of the human monoamine oxidase B (Chain B) showing the co- crystallized ligand at the ligand binding site (red).

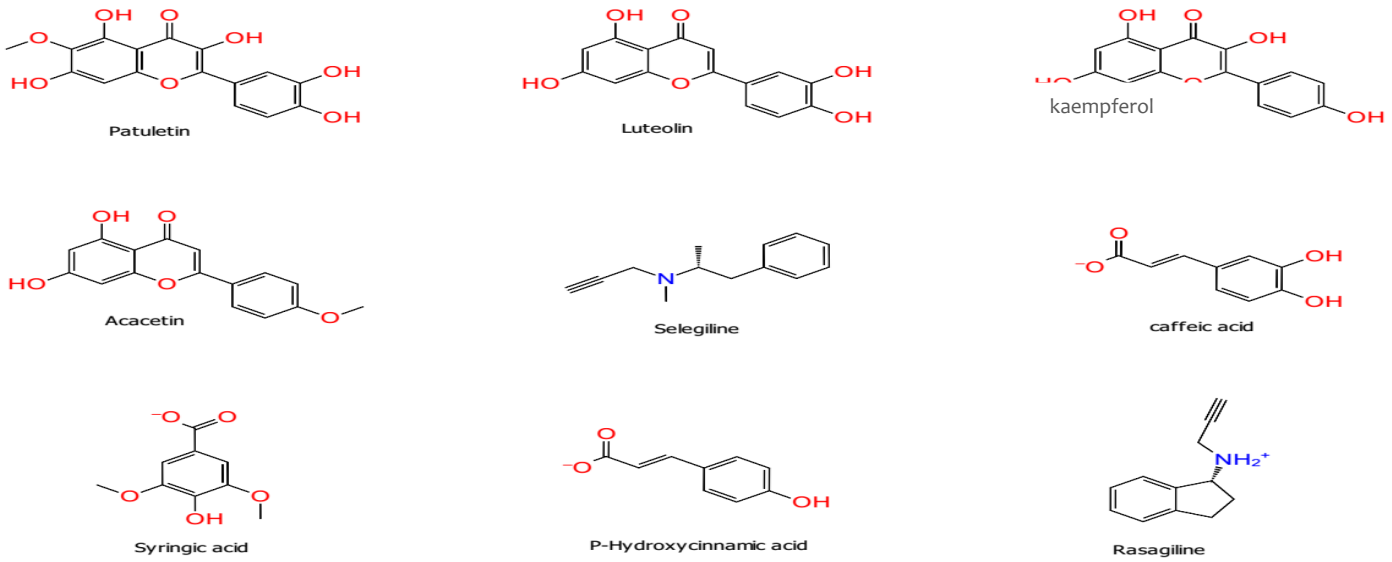


Figure 2: 2Dimentional structure of selected phyto-constituents of *B. pinnatum*

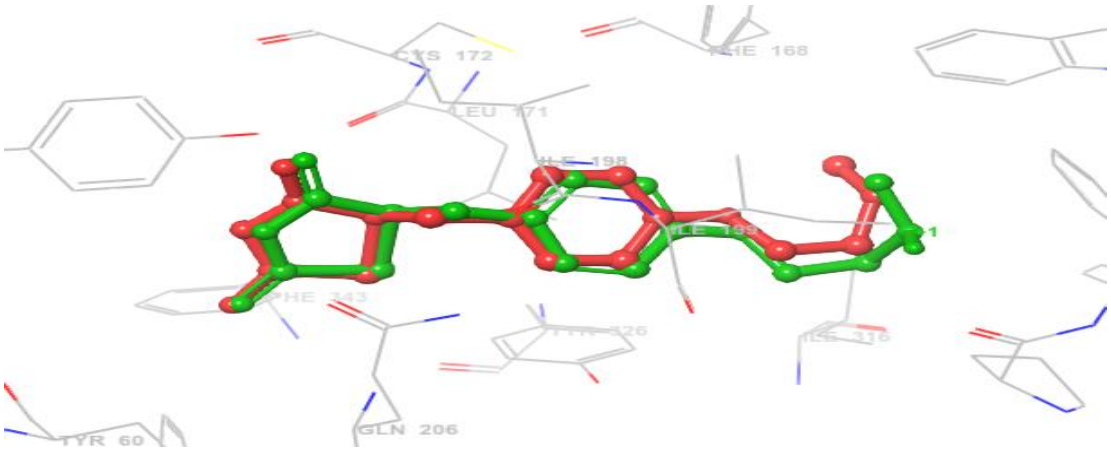


Figure. 3: Validation of docking: Comparability of the re-docked binding mode (green) and the co-crystallized pose (red) of rosiglitazone with the accompany residues of MAO-B binding pocket.

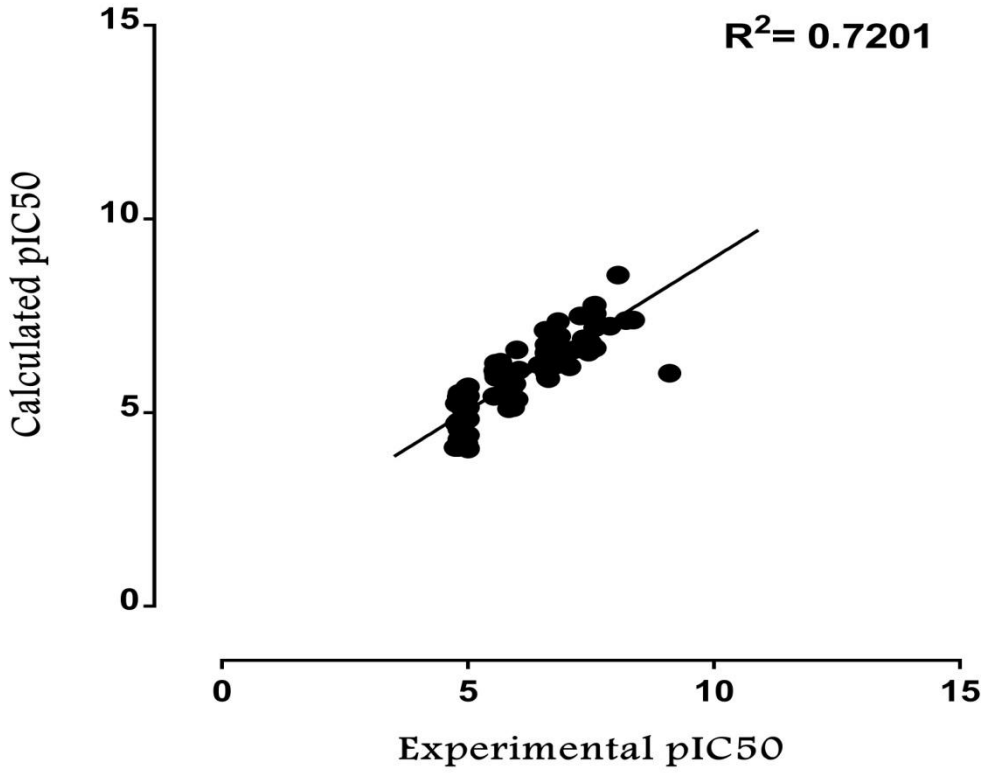
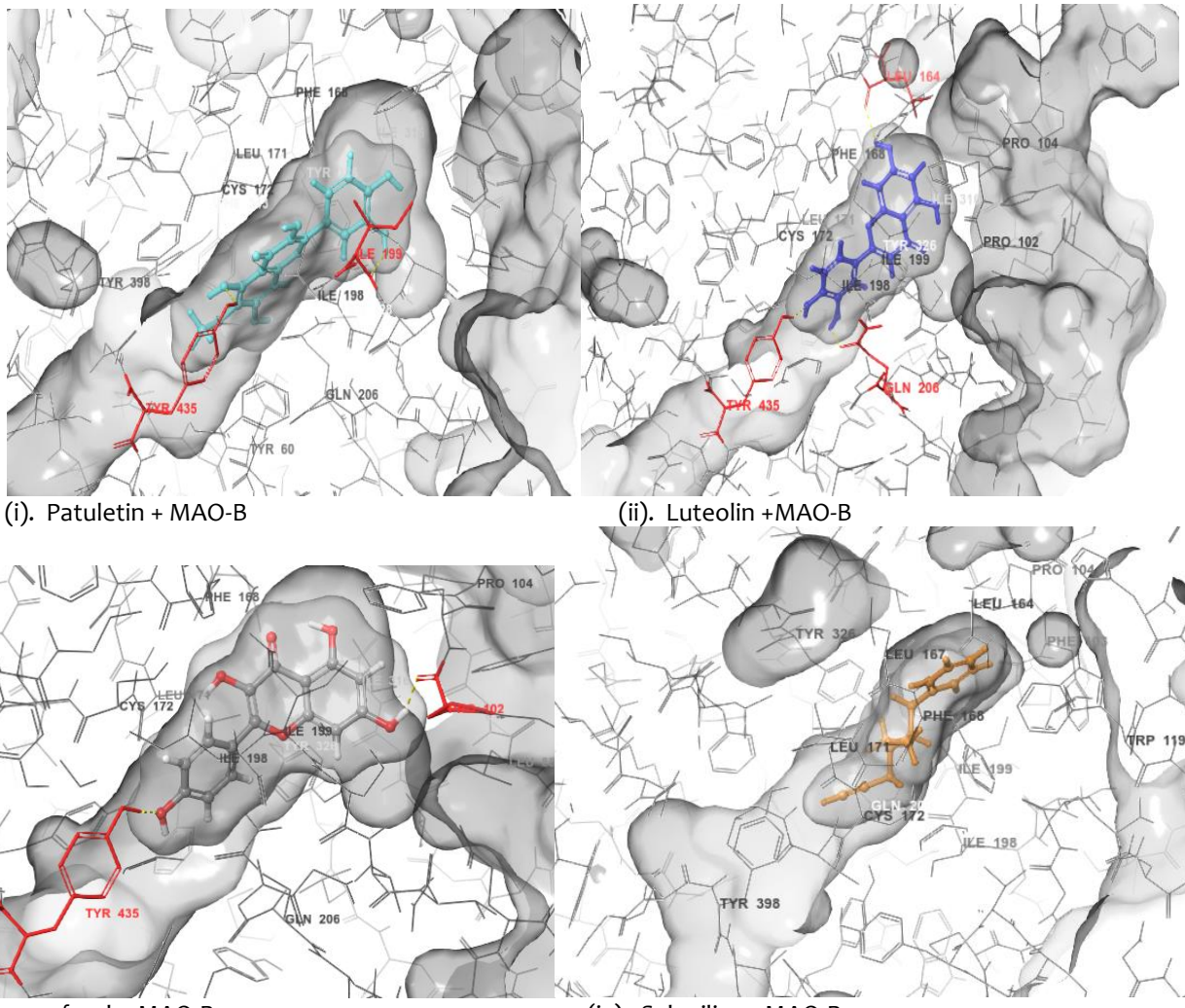


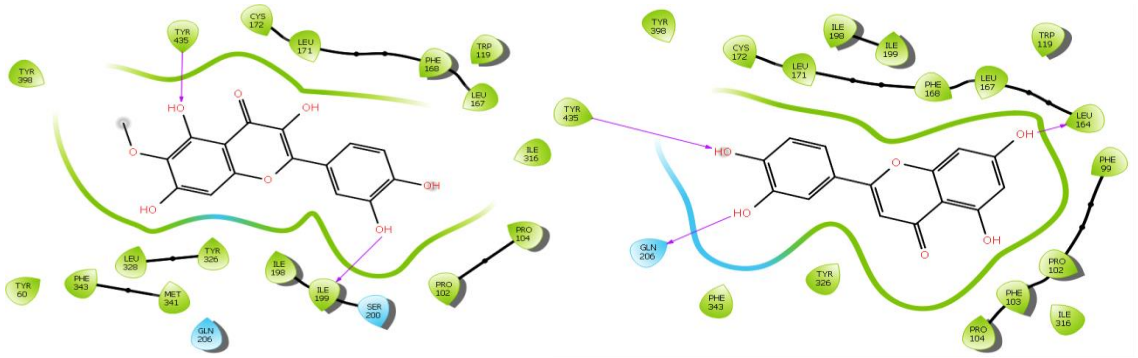
Figure. 4. Correlation coefficient graph of docking scores of various inhibitors of Monoamine Oxidase B receptor (MAO-B) and their corresponding experimental pIC50 values. The inhibitors (compounds) and their corresponding pIC50 (experimentally derived IC50) were downloaded from the ChEMBL database, the strong correlation (0.72) between the Calculated IC50 and pIC50 shows that computer can reproduce experimental values and this gives credence to the docking scores generated, in the present study.



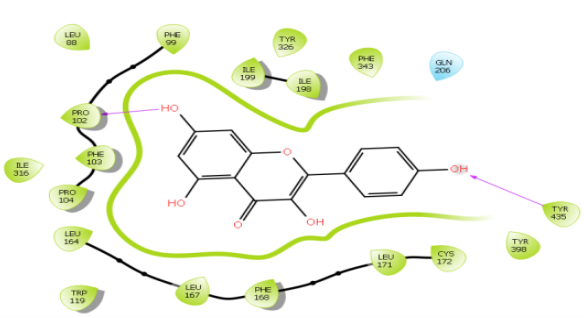
(i). Patuletin + MAO-B (ii). Luteolin +MAO-B

(iii) Kaempferol + MAO-B (iv). Selegiline +MAO-B

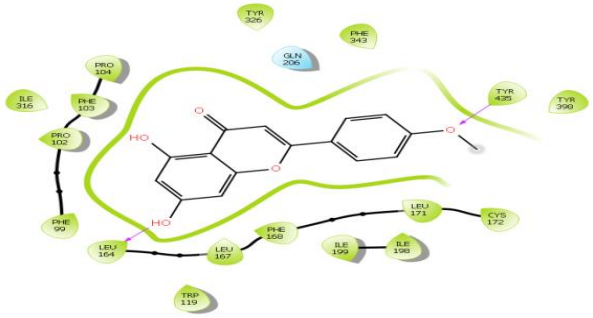
Figure 5: 3-Dimensional models of docked complexes showing interactions of selected compounds in the active site of the target enzyme MAO-B



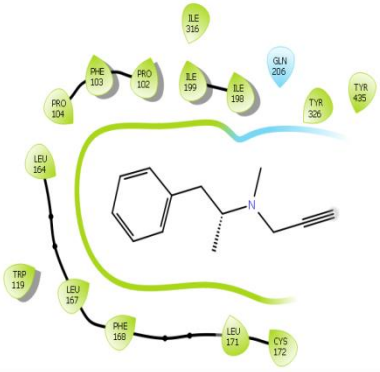
(i). Patuletin + MAO-B (ii).Luteolin +MAO-



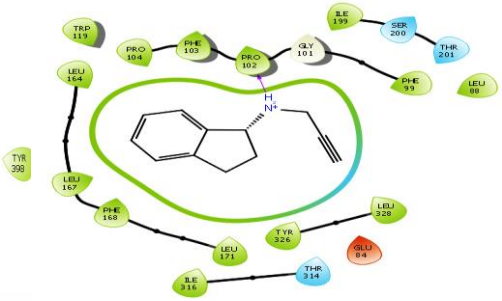
(iii). Kaempferol



(iv). Acacetin



(v). Selegiline +MAO-B



(vi). Rasagiline + MAO-B

Figure 6(i-vii): 2-Dimentional representations of molecular interactions within the binding pocket of MAO-B and phyto-ligands