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Bioinformatics Based: in Silico Docking Analysis of Polyherbal Formulation for The Management of Parkinson's Disease (Nadukku Vatham)

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Abstract

Background: *The discipline of Siddha medicine, particularly herbal formulations, can benefit greatly from the use of molecular docking because it enables the molecular interactions of the formulation's lead molecules with receptors to be understood, as well as the inference of the formulation's basic biochemical targets.* ***Aim:*** *The goal of this study is to carry out an In-silico computational analysis of the phytochemicals found in Kuruver Kudineer (KK), a traditional Siddha remedy that is used for managing behavioral deficit in Parkinsons disease.* ***Methodology:*** *The ligand structures were developed and optimized using Auto Dock Tools (Morris, Goodsell et al., 1998). Using Auto dock Vina, the compounds were all docked. The function of the target protein Monoamine Oxidase -A (PDB 2Z5X), which is involved in the breakdown of the neurotransmitters by MAO-A, will be inhibited by the creation of a hydrogen bond between phytocomponents and the target's core amino acids (Tyr 69, Ile 335, Tyr 407, and Tyr 444). In order to control the dopamine level, phytocomponents that inhibit the target enzyme MAO-A may be used as potential targets.* ***Results:*** *The compounds present in Kuruver Kudineer (KK) like Gingerenone-A, Betulinic acid, Zingiberene, Rutin, Geniposide and β-sitosterol showed maximum interactions with MAO –A when compared to that of Clorgyline. According to the outcomes of the computational investigation, the bio-active substances present in the Siddha formulation Kuruver Kudineer (KK) have significant affinity to the target MAO-A (PDB 2Z5X).* ***Conclusions****: From the results of the present study, it was concluded that the MAO – A reveal significant effect to managing the behavioral deficit and thereby considered an excellent drug choice for the clinical management of Parkinson's disease (Nadukku vatham)*

Keywords: *Siddha medicine, Parkinsons disease, Nadukku vatham, Kuruver Kudineer, Monoamine oxidase (MAO), Molecular Docking*

1. Introduction

The discipline of Siddha medicine, and herbal formulations in particular, can greatly benefit from the use of the molecular docking technique because it makes it possible to comprehend the molecule-to-

molecule interactions of the formulation's lead molecules with receptors and to infer the formulation's fundamental biochemical targets. James Parkinson, an English physician, coined the term "the shaking palsy" to describe Parkinson's disease (PD) for the first time in 1817. Parkinson's disease was later named in his esteem. The senses and intellects are unaltered, and the disease manifests as "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward and to pass from a walking to a running pace."

After Alzheimer's disease (AD), Parkinson's disease (PD) is the most prevalent neurodegenerative condition. Older adults are more likely to experience it. One percent of persons over 60 are affected, while older age groups are more frequently affected. Male and female sexes are equally impacted Dopaminergic neurons in the substantia nigra are the source of the neurotransmitter, and their degeneration is the fundamental disease. A balance exists between acetylcholine and dopamine in most people. Parkinsonism is caused by a collection of nerve cells located deep inside the Centre of the brain, in a region known as the substantia nigra, which become hyperactive when dopamine levels decrease.

The clinical manifestation of Parkinson's disease is roughly associated with the ailment known as Nadukku vatham in traditional Siddha treatment. Only for the purpose of treating the condition, several herbal or herbal-mineral formulations have been used. One herbal remedy that is utilized for this illness is Kuruver Kudineer (KK). Our Siddha literature mentions the formulation. Siddha medicine has historically used these five elements to address many of the disease's consequences.

Monoamine Oxidase (MAO-A)

In the outer membrane of mitochondria in cells, monoamine oxidase (MAO), a flavin-dependent enzyme, is frequently placed. Two well-known MOA subtypes, MAO-A and MAO-B, differ in terms of tissue distribution, substrate and inhibitor sensitivity, and three-dimensional structural characteristics but share up to 72% of their sequences. By oxidative breaking down the substrate, they are crucial in the oxidative deamination of crucial amine neurotransmitters and dietary amines. It also participates in the completion of this phase in the central and peripheral nervous systems (CNS and PNS) by deoxidizing FAD with molecule oxygen and simultaneously releasing H_2O_2.

Compounds that inhibit MAO-A activity have an antidepressant effect by primarily boosting norepinephrine and serotonin (5HT), whereas MAO-B inhibitors have an antiparkinsonian effect by primarily raising dopamine. In experimental study, the distinct functions of Tyr 69, Ile 335, Tyr 407, and Tyr 444 in the finding of particular substrates and inhibitors for human MAO-A and MAO-B have been widely established. A molecular docking simulation technique was used in this investigation to predict powerful MAO-A enzyme inhibitors, followed by lead compound discovery. The inhibition of the MAO-A enzyme by natural and synthetic substances has previously been explored using a variety of methodologies. However, no effective reversible inhibitor of this enzyme has yet to be discovered, necessitating further investigation. MAO is a key regulator of the neurotransmitter serotonin, nor –epinephrine and dopamine abnormalities of which has been linked to Parkinsons diseaseAs a result, the purpose of this study was to suggest a prospective MAO-A inhibitor that could be utilized for this disease. Here I chose Inhibitors of MAO-A Phytocomponents in this study (5). The major aim of the study was to evaluate an in-silico computational analysis of the phytochemicals found in Kuruver Kudineer (KK), a traditional Siddha remedy that is widely used to managing Parkinsons disease (Nadukku vatham).

2. Materials And Methods

Test drug Kuruver Kudineer (KK)

Kuruver Kudineer (KK) is a poly-herbal siddha formulation with active compounds that are used to managing Parkinsons disease (Naduku vatham). The following Siddha medicinal herbs are included in this Kuruver Kudineer Preparation (Table 1)

Table 1: Ingredients of Kuruver Kudineer with its botanical name and phyto-components selected for docking

S.No	Vernacular Name	Botanical Name	Phyto- Components
1.	Kuruver	*Vetiveria zizanioides*	β-vetivenene (6)
2.	Vilamichu	*Plectranthus vettiveroides*	Thymol (7)
3.	Chukku	*Zingeber officinale*	Gingerenone-A (8) Zingiberene (8)
4.	Parpadagam	*Hedyotis corymbosa*	Rutin (9) Geniposide (9)
5.	Siruthaekku	*Clerodendrum Serratum*	β-sitosterol (10)

			Betulinic acid (10)

Target protein retrieval

Binding of phytocomponents with the core amino acids (**Tyr 69, Ile335**, **Tyr407, Tyr444**) of the target by forming hydrogen bond will hinder the function of the enzyme Monoamine oxidase A- (MAO-A) with PDB –2Z5X. These amino acid residues are functionally responsible for binding of substrate and further involved in degradation of the neurotransmitter dopamine by MAO-A. Thereby phytocomponents which inhibit the target enzyme MAO-A may act as a potential therapeutic agent for management of Parkinsons disease (Naduku vatham). The crystalline structure of the target protein Monoamine oxidase-A (PDB 2Z5X) was obtained from the protein data bank, and the protein was cleaned up and missing hydrogen atoms were replaced. The Auto dock programme examined the different orientations of the lead molecules in relation to the target protein, and the best dock position was chosen based on the interaction study analysis.

Fig 1: 3D- Structure of Monoamine oxidase A (PDB) - 2Z5X

Ligand preparation

β-vetivenene, Thymol, Gingerenone-A, Zingiberene, Rutin, Geniposide, β-sitosterol, Betulinic acid were reported as bioactive phytocomponents in the siddha formulation Kuruver Kudineer. For docking investigations, the 3D structural coordinates of these 8 bioactive phytochemicals acquired from chem were used. Using chem draw prof online tool version 12.0., these ligand structures were further optimized and prepared

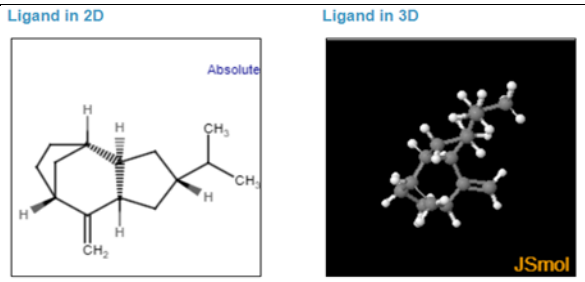
Protein-ligand docking

The crystal structure of the Monoamine oxidase-A enzyme protein-ligand complex ((PDB 2Z5X) was obtained from online repository of Protein Data Bank. The 3D protein structures were optimized and prepared using chem draw prof online tool version 12.0

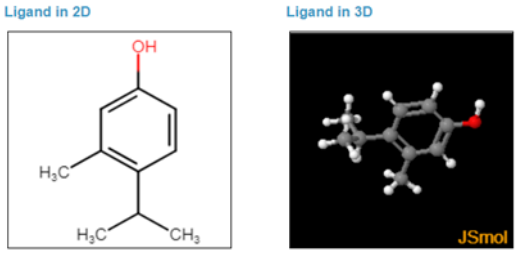
Molecular Docking methodology

Docking calculations were carried out for retrieved phytocomponents against target enzyme Monoamine oxidase A. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (*Morris, Goodsell et al., 1998*). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (*Morris, Goodsell et al., 1998*). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (*Solis and Wets, 1981*). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

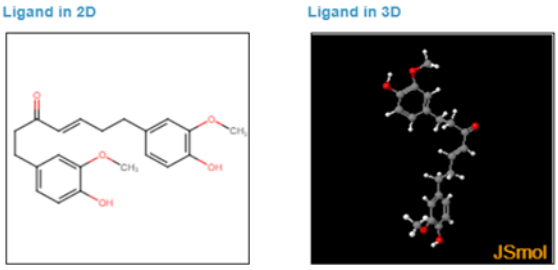
Fig 2: 2D and 3D Structure of Phytocomponents



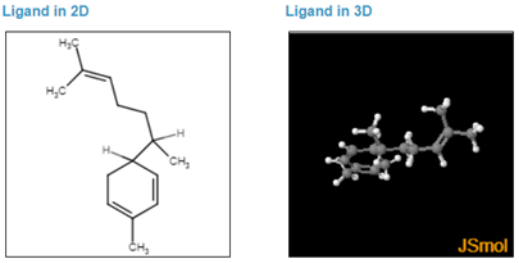
β-vetivenene



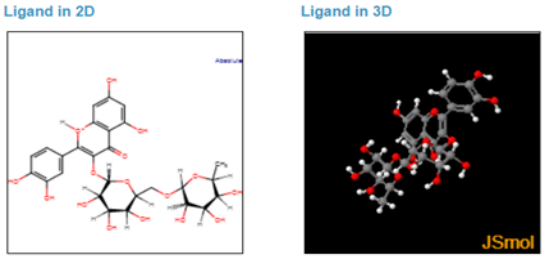
Thymol



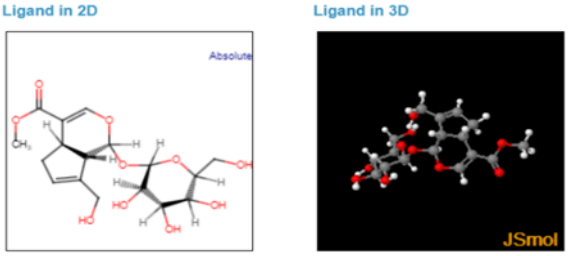
Gingerenone-A



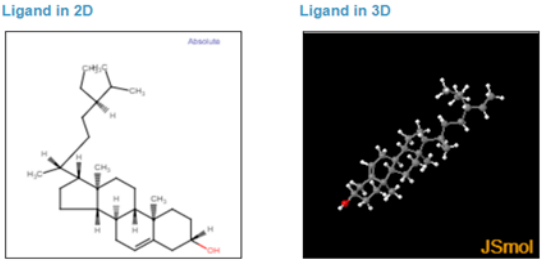
Zingiberene



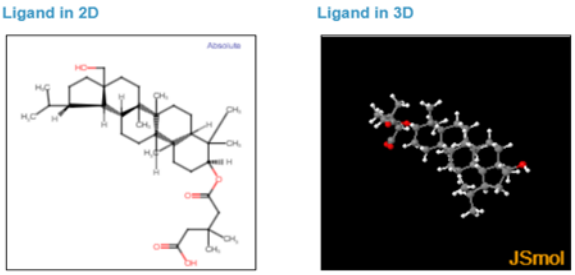
Rutin



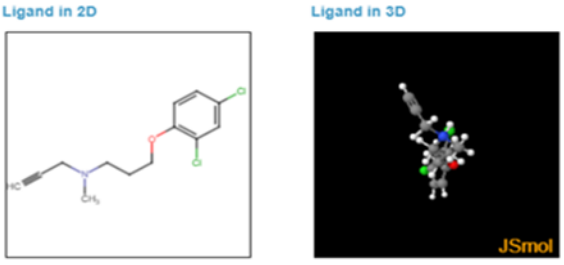
Geniposide



β-sitosterol



Betulinic acid



Clorgyline

Table 2: Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
β-vetivenene	202.33 g/mol	$C_{15}H_{24}$	0	0	0
Thymol	150.221 g/mol	$C_{10}H_{14}O$	1	1	1
Gingerenone-A	356.4 g/mol	$C_{21}H_{24}O_5$	2	5	9
Zingiberene	204.35 g/mol	$C_{15}H_{24}$	0	0	4
Rutin	610.5 g/mol	$C_{27}H_{30}O_{16}$	10	16	6
Geniposide	388.4 g/mol	$C_{17}H_{24}O_{10}$	5	10	6
β-sitosterol	414.7g/mol	$C_{29}H_{50}O$	1	1	6
Betulinic acid	456.7 g/mol	$C_{30}H_{48}O_3$	2	3	2
Clorgyline	272.17 g/mol	$C_{13}H_{15}Cl_2NO$	0	2	6

3. Results and Discussion

The plants used in the siddha formulation Kuruver Kudineer yielded a total of 8 bioactive lead components. According to the herb's provided data, phytochemicals such as Gingerenone-A and Betulinic acid have a maximum of four interactions (100%) with the target protein enzyme Monoamine oxidase A's core active amino acid residues. Following this, compounds such as Zingiberene, Rutin, Geniposide, and -sitosterol placed second with the highest number of interactions (75%) with the active site of the target enzyme Monoamine oxidase A, compared to standard Clorgyline, which reveals the highest number of interactions (four).

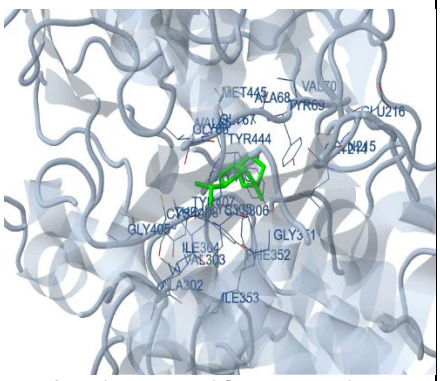
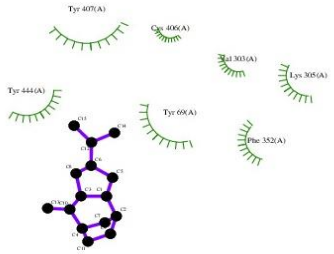
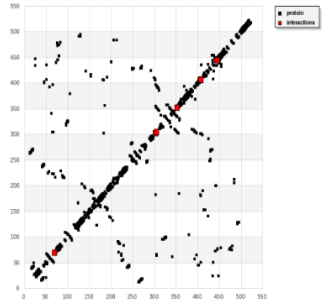
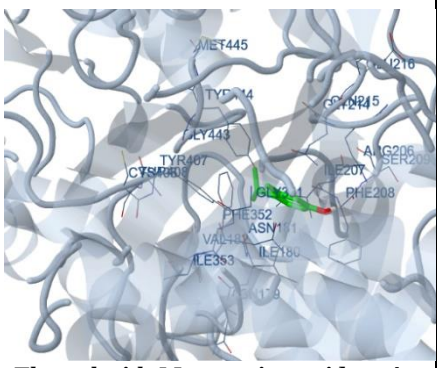
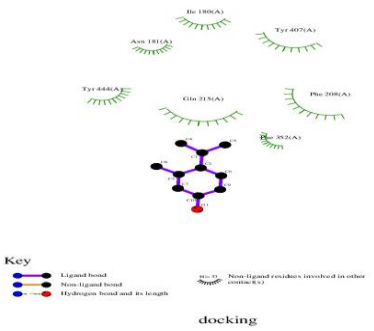
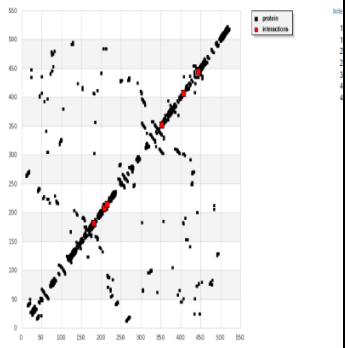
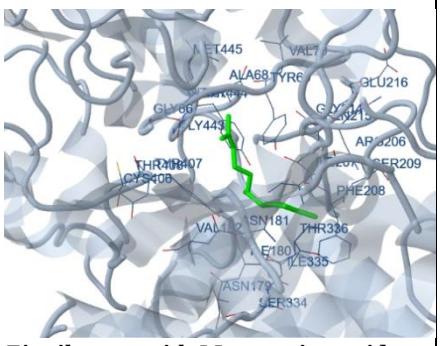
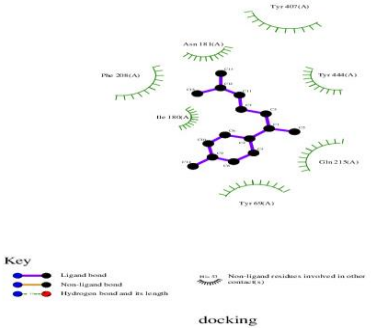
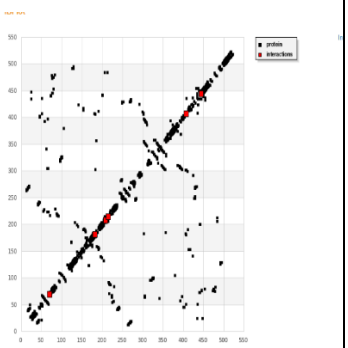
Table 3: Summary of the molecular docking studies of compounds against Monoamine oxidase A- (MAO-A) with PDB – 2Z5X

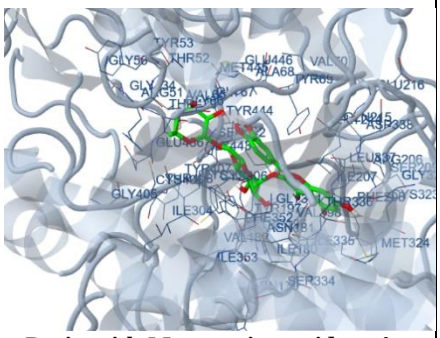
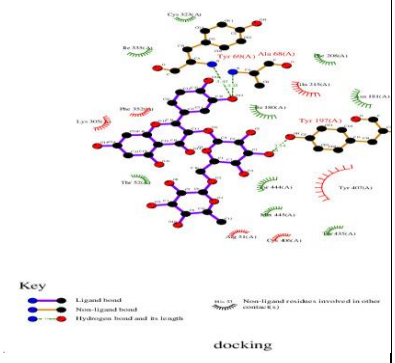
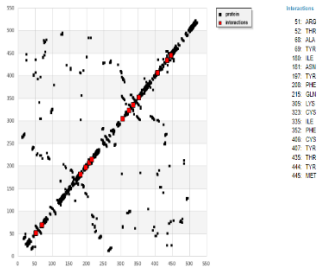
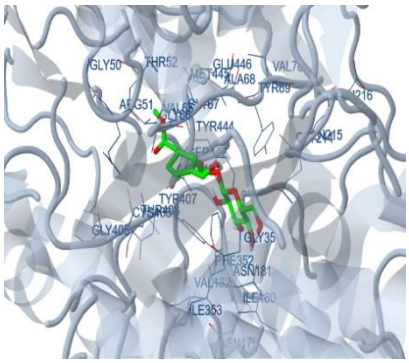
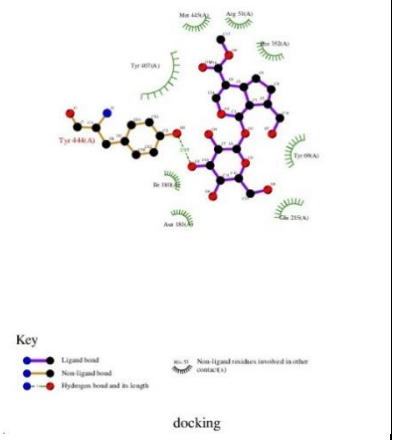
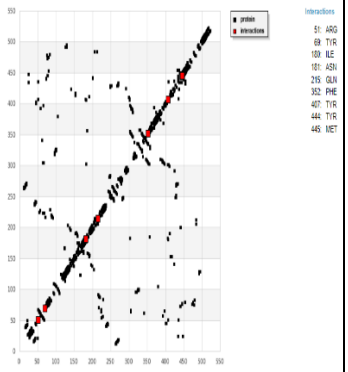
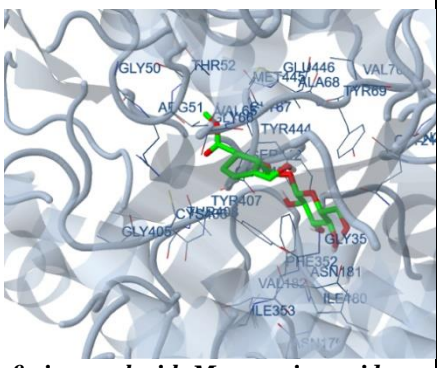
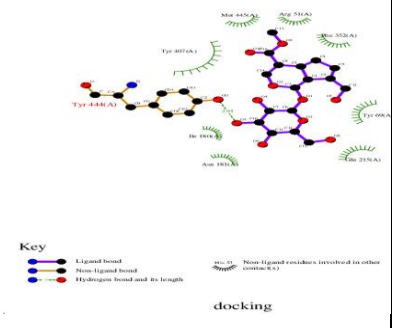
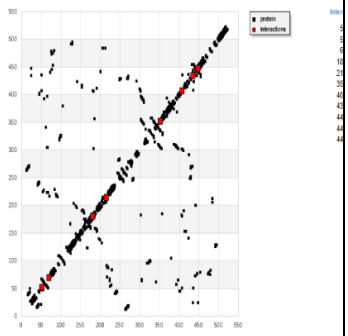
Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
β-vetivenene	-8.31 kcal/mol	804.38 nM	-0.09 kcal/mol	-8.61 kcal/mol	593.075
Thymol	-5.52 kcal/mol	89.43 uM	-0.07 kcal/mol	-6.15 kcal/mol	480.183
Gingerenone-A	-10.17 kcal/mol	34.82 nM	-0.04 kcal/mol	-11.38 kcal/mol	919.896
Zingiberene	-8.24 kcal/mol	909.28 nM	-0.11 kcal/mol	-9.31 kcal/mol	644.046
Rutin	-6.70 kcal/mol	12.30 uM	-0.05 kcal/mol	-7.58 kcal/mol	594.645
Geniposide	-11.17 kcal/mol	6.49 nM	-0.06 kcal/mol	-10.61 kcal/mol	851.104
β-sitosterol	-12.54 kcal/mol	644.68 pM	-0.02 kcal/mol	-14.29 kcal/mol	1013.384
Betulinic acid	-6.54 kcal/mol	16.03 uM	-0.18 kcal/mol	-10.33 kcal/mol	1156.21
Clorgyline	-8.46 kcal/mol	631.47 nM	-0.05 kcal/mol	-9.39 kcal/mol	711.724

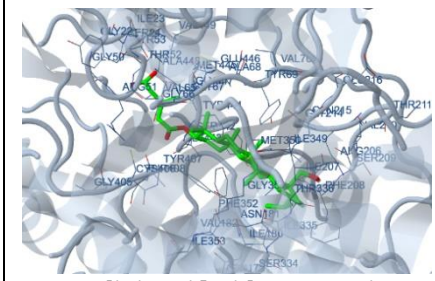
Table 4: Amino acid Residue Interaction of Lead against Monoamine oxidase A- (MAO-A) with PDB – 2Z5X

Compounds	Interactions	Amino Acid Residues																	
β-vetivenene	3	69 TYR	303 VAL	305 LYS	352 PHE	406 CYS	407 TYR	444 TYR											
Thymol	2	180 ILE	181 ASN	208 PHE	215 GLN	352 PHE	407 TYR	444 TYR											
Gingerenone-A	4	69 TYR	180 ILE	181 ASN	208 PHE	215 GLN	305 LYS	335 ILE	337 LEU	350 MET	352 PHE	406 CYS	407 TYR	444 TYR					
Zingiberene	3	69 TYR	180 ILE	181 ASN	208 PHE	215 GLN	407 TYR	444 TYR											
Rutin	3	51 ARG	52 THR	68 ALA	69 TYR	180 ILE	181 ASN	197 TYR	208 PHE	215 GLN	305 LYS	323 CYS	335 ILE	352 PHE	406 CYS	407 TYR	435 THR	444 TYR	445 MET
Geniposide	3	51 ARG	69 TYR	180 ILE	181 ASN	215 GLN	352 PHE	407 TYR	444 TYR	445 MET									
β-sitosterol	3	51 ARG	52 THR	69 TYR	180 ILE	215 GLN	352 PHE	407 TYR	435 THR	444 TYR	445 MET	448 ALA							
Betulinic acid	4	23 ILE	51 ARG	52 THR	69 TYR	180 ILE	181 ASN	208 PHE	210 VAL	215 GLN	335 ILE	352 PHE	406 CYS	407 TYR	444 TYR	445 MET	448 ALA		
Clorgyline	4	69 TYR	180 ILE	181 ASN	208 PHE	215 GLN	335 ILE	352 PHE	407 TYR	444 TYR									

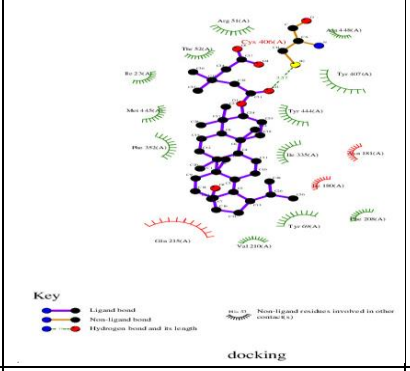
Fig 3: Docking Pose

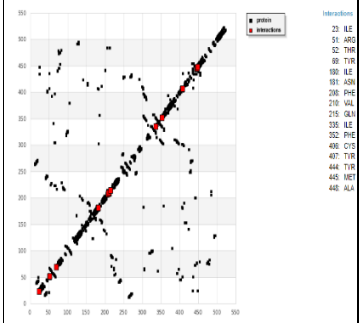
Ligand with MAO-A -2Z5X	2D Interaction plot analysis	Hydrogen bond plotting with core Amino acid Analysis
 *β-vetivenene with Monoamine oxidase A- (MAO-A) – 2Z5X*		
 *Thymol with Monoamine oxidase A- (MAO-A) – 2Z5X*		
 *Zingiberene with Monoamine oxidase A- (MAO-A) – 2Z5X*		

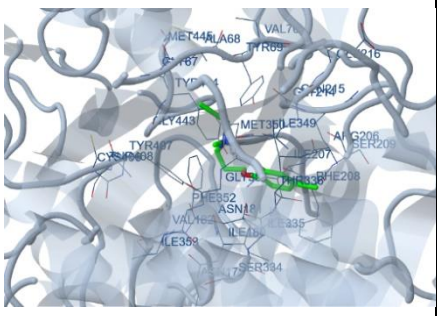
 ***Rutin with Monoamine oxidase A- (MAO-A) – 2Z5X***	 	
 ***Geniposide with Monoamine oxidase A- (MAO-A) – 2Z5X***	 	
 ***β-sitosterol with Monoamine oxidase A- (MAO-A) – 2Z5X***	 	



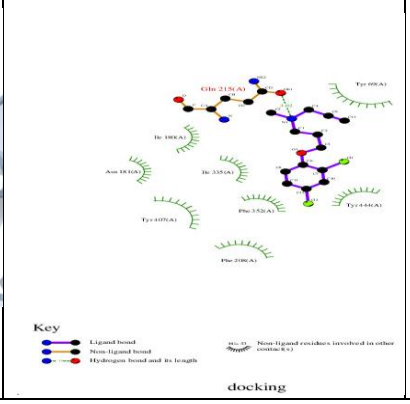
Betulinic acid with Monoamine oxidase A- (MAO-A) – 2Z5X

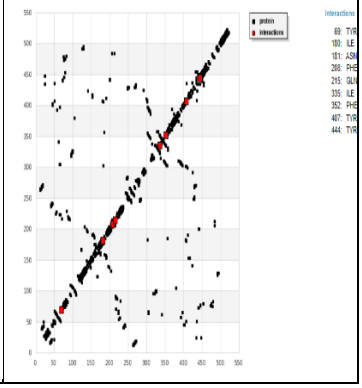






Clorgyline with Monoamine oxidase A- (MAO-A) – 2Z5X





4. Conclusion

Based on the results of the computational analysis it was concluded that the bio-active compound's like Gingerenone-A, Betulinic acid, Zingiberene, Rutin, Geniposide and β-sitosterol present in the siddha formulation Kuruver Kudineer possess significant binding against the target Monoamine oxidase A by interacting with active amino acid present on the active site thereby it was concluded that these compounds may exerts promising anti-parkinson's activity by inhibiting the enzyme Monoamine oxidase A thereby it prevent the degradation of the vital neurotransmitter dopamine essential for neuron function. As a result, phytocomponents that inhibit the target Monoamine Oxidase A may be useful in the treatment of Parkinsons disease (Naduku vatham). It was concluded that the phytochemicals found in the herb Kuruver Kudineer have strong anti-parkinson's activity.

Ethics approval

Not Applicable

Consent to participate and consent for publication:

Not Applicable

Competing interests

The Authors have no competing interests to declare

Authors contributions:

Conceptualization, supervision, Methodology, Data interpretation, Original Data preparation, Writing, reviewing, editing done. All the Authors read and approved the final manuscript

Availability of Data and materials:

We declare that all the data generated are included in this study.

Conflict of Interest:

The authors declare that there is no conflict of interest.

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