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COMPUTATIONAL EVALUATION OF PARANGIPATTAI KASAYAM TARGETING GABA RECEPTORS FOR SPASTICITY MANAGEMENT IN CEREBRAL PALSY (SIRAKAMBAVATHAM) – A MOLECULAR DOCKING STUDY

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ABSTRACT :

BACKGROUND:

The Siddha system of medicine, one of the world's oldest traditional healing practices, is renowned for its holistic approach, addressing not just physical ailments but also mental and spiritual well-being. Siddha system classifies diseases into 4448 types. Among them is Vatha diseases which were subdivided into 80 types. Sirakambavatham one among them is compared with Cerebral palsy a neurological disorder that affects movement, muscle tone and posture. Early intervention and ongoing support can greatly improve outcomes for individual child with Cerebral palsy. This article explains in detail about the molecular docking analysis of Parangipattai kasayam against GABA receptors in management of spasticity in Cerebral palsy children.

AIM & OBJECTIVE:

To evaluate the efficacy of Parangipattai Kasayam against GABA receptors in management of spasticity in Cerebral palsy through molecular docking analysis.

MATERIALS AND METHODS:

Parangipattai kasayam was mentioned in Siddha literature Pillaipini vagadam Part-2 to manage all vatha diseases was taken for the study to evaluate the property of reducing spasticity. A well-defined in silico computational study of the selected Compounds using various bioinformatics software such as Chem3D pro 12.0, MGL AutoDock Tools, AutoDock Vina, Molegro Molecular Viewer, Discovery Studio Visualizer. Online resources such as RCSB-Protein Data Bank(PDB), PubChem database, SwissADME, Active site prediction tool, etc., were used in this study. Overall, the molecular docking provide a computational framework for predicting and analyzing ligand-receptor interactions, facilitating drug discovery.

RESULT:

From the molecular docking study three compounds had docking score more than -8.0 kcal/mol, nine compounds had -7 to -8 kcal/mol, eleven compounds had -6 to -7 kcal/mol and fourteen compounds had -5 to -6 kcal/mol with the GABA receptor protein. The present insilico study shows that phytochemicals of Parangipattai kasayam shows that the number of phyto compounds and standard drug Baclofen had no violation of Lipinski rule of five. Out of forty six compounds selected 34 phytochemicals had no Lipinski violation, 8 phytochemical had one violation, 3 phytochemical had two violations and one phytochemical had three violations.

CONCLUSION:

Based on the insilico study of Parangipattai kasayam it was concluded that the bioactive compounds of this polyherbal medicine possess significant binding affinity against the target GABA receptors. Hence, it was proved that Parangipattai kasayam enhances the muscle relaxant property against the GABA receptors by supporting the Cerebral palsy children to manage the spasticity.

KEY WORDS: Sirakambavatham, Parangipattai kasayam, GABA receptor.

INTRODUCTION:

Cerebral palsy (CP) is a neurological disorder characterized by motor impairment and often accompanied by spasticity, which significantly impacts the quality of life of affected individuals. Spasticity, a condition marked by increased muscle tone and stiffness, contributes to difficulties in movement and coordination, posing challenges in daily activities. Despite various treatment modalities available, there is a need for novel therapeutic approaches to effectively manage spasticity in CP. Parangipattai Kasayam, a traditional herbal formulation used in Siddha medicine, has gained attention for its potential therapeutic effects in neurological disorders. It contains a combination of herbs known for their neuroprotective and muscle relaxant properties. One promising avenue for its application is through its interaction with gamma-aminobutyric acid (GABA) receptors. GABA receptors are key mediators of inhibitory neurotransmission in the central nervous system and play a crucial role in regulating muscle tone. Modulation of GABA receptor activity can lead to muscle relaxation, offering a potential mechanism for alleviating spasticity in CP. Molecular docking, a computational technique, provides valuable insights into the interaction between small molecules and target receptors at the molecular level. By simulating the binding of Parangipattai Kasayam components to GABA receptors, molecular docking analysis can predict the likelihood and strength of their interactions, aiding in the identification of potential therapeutic candidates. In this study, we present a molecular docking analysis of Parangipattai Kasayam constituents against GABA receptors, aiming to elucidate their binding affinities and potential as spasticity management agents in cerebral palsy. This research contributes to the exploration of alternative treatment strategies for improving the quality of life of individuals with CP.

Materials and methods:

The Parangipattai kasayam, mentioned in Siddha literature Pillaipini Vagadam Part-2, is known for managing various vatha diseases. The current study was aimed to evaluate its potential in reducing spasticity. They conducted a comprehensive computational analysis using various bioinformatics software tools. Firstly, Chem3D Pro 12.0 was employed to generate molecular structures of the selected compounds. Then, MGL AutoDock Tools and AutoDock Vina were utilized for molecular docking studies, predicting the binding interactions between the compounds and target receptors. To visualize the results, tools like Molegro Molecular Viewer and Discovery Studio Visualizer were employed, to analyze the ligand-receptor interactions in detail. In addition to these software tools, the study also utilized online resources such as the RCSB-Protein Data Bank (PDB) and PubChem database for obtaining protein structures and compound information. SwissADME was utilized for assessing the pharmacokinetic properties of the compounds. Furthermore, an active site prediction tool was used to identify potential binding sites on the target receptors. Overall, molecular docking provided a computational framework for predicting and analyzing ligand-receptor interactions, which can greatly facilitate the process of drug discovery and development.

Computational tools and Web servers:

A well-defined *in silico* computational study of the selected Compounds using various bioinformatics software such as Chem3D pro 12.0, MGL AutoDock Tools, AutoDock Vina, Molegro Molecular Viewer, Discovery Studio Visualizer. Online resources such as RCSB-Protein Data Bank(PDB), PubChem database, SwissADME, Active site prediction tool, etc., were used in this study.[1-5]

ADMET study:

The Absorption, Distribution, Metabolism and excretion (ADME) properties of the compounds were performed using SWISSADME online server. The Drug likeness property was evaluated by Lipinski's rule of five. According to the Lipinski rule of five, molecular weight should be less than 500 daltons, Hydrogen bond donor should be less than 5, Hydrogen bond acceptor should be less than 10 and Partition coefficient (LogP) should be less 5.[6,7]

Protein and Ligand Preparation:

The drug target proteins were retrieved from the RCSB-PDB database with higher resolution. The Crystal structure of GABA(B) receptor (PDB ID 4MS4) was predicted by X-ray diffraction method, resolution with 1.90 Å. The retrieved proteins were prepared by removal of cocrystallized ligand and water molecules using Molegro Molecular Viewer and saved as the PDB file format. The fourty six ligand molecules SMILES were obtained from Pubchem database. The 2D structure of Ligand molecules was sketched by Chemsketch software and saved in mol file format. These sketched structures of the ligand molecules were energy minimized by Chem3D pro 12.0 software and saved as the PDB file format. The Physicochemical properties of the molecules were calculated using SWISSADME online server.[8-12]

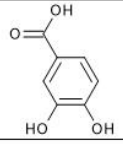
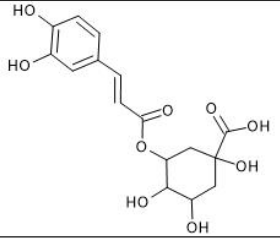
Activite site prediction and Molecular docking:

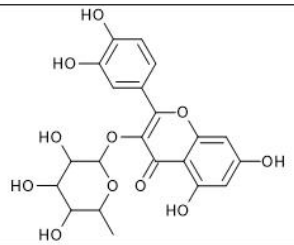
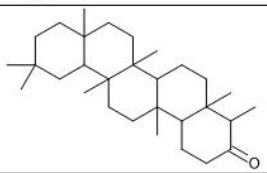
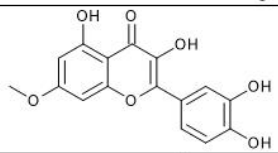
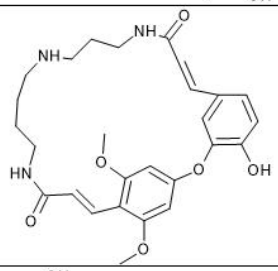
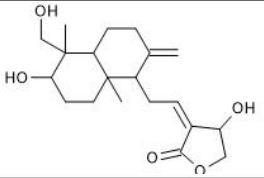
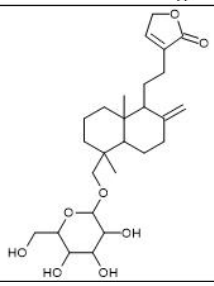
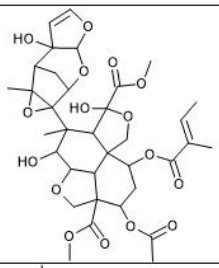
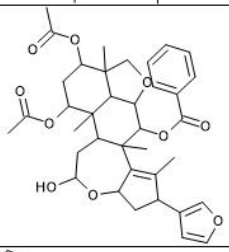
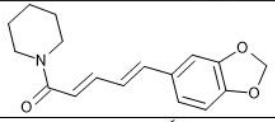
The Active site of the selected two target proteins was predicted by the Supercomputing Facility for Bioinformatics & Computational Biology, IIT Delhi. The phytochemical compounds of the Parangipattai Kasayam were docked to GABA receptor of drug target protein. The molecular docking to find the potential binding affinity of phytochemical compounds with target protein. The molecular docking of the ligands with the target proteins involves the following steps, Protein Preparation, Ligand Preparation, Grids Generation and ligand docking. The molecular docking of the drug target was performed using AutoDock Vina. The Binding interaction of the protein-ligands complex was visualized and analyzed using Biovia Discovery Studio visualizer 2021.[14,15]

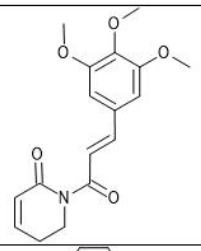
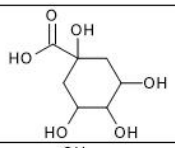
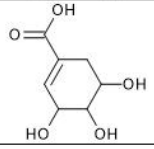
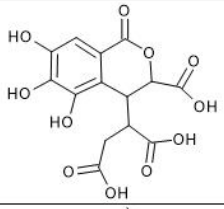
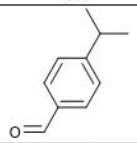
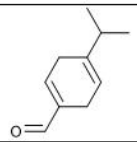
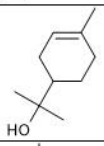
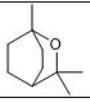
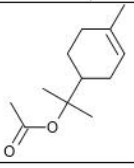
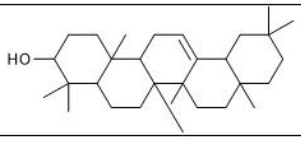
Table No.1 The list of plants and its phytocompounds

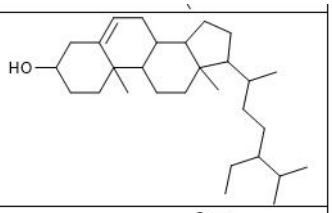
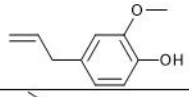
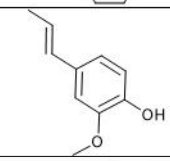
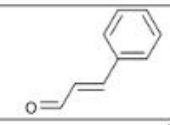
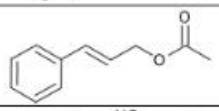
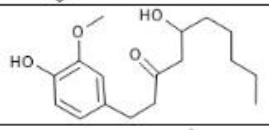
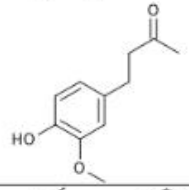
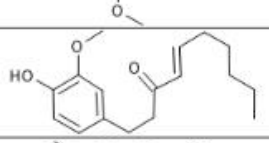
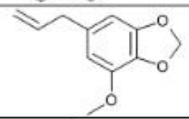
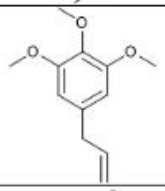
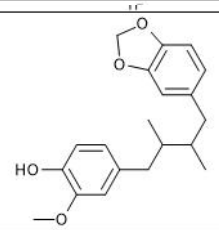
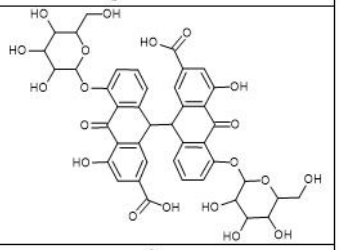
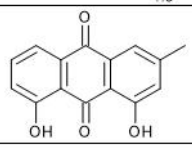
S.No	Plant Name	Phytoconstituent
1.	Smilax china (Parangipattai)	Protocatechuic acid, 5-O-Caffeoylquinic acid, Quercitrin
2.	Azima tetracantha (Sangam verpattai)	Friedelin, Rhamnetin
3.	Capparis decidua (Sengathari)	Capparisinine, Codonocarpine
4.	Andrographis paniculata (Nilavembu)	Andrographolide, Neoandrographolide
5.	Azadirachta indica (Veppam pattai)	Azadirachtin, Nimbolinin A
6.	Piper longum (Thippili)	Piperine, Piperlongumine
7.	Piper nigrum (Milagu)	Piperidine, Pyrrolidine
8.	Terminalia bellerica (Thandripattai)	Quinic acid, Chebulic acid, Shikimic acid
9.	Cuminum cyminum (Seeragam)	Cumin aldehyde, p-Mentha-1,4-dien-7-al
10.	Elettaria cardamomum (Elam)	Alpha-Terpineol, Eucalyptol, Alpha-Terpinyl acetate
11.	Messua ferrea (Sirunagapoo)	Beta-Amyrin, β-sitosterol
12.	Eugenia caryphyllata (Lavangam)	Eugenol, Isoeugenol
13.	Cinnamomum zeylanicum (Lavangapattai)	Cinnamaldehyde, Cinnamyl acetate
14.	Zingiber officinale (Sukku)	Shogaol, Zingerone, Gingerol
15.	Myristica fragrans (Jathikai)	Myristicin, Elemicin, Macelignan
16.	Casia fistula (Lavanga pathiri)	Chrysophanol, Sennosides, Kaempferol
17.	Alpinia galanga (Arathai)	Galangal acetate, beta-Sitosterol-d-glucoside, Alpha-Bergamotene
18.	Saussurea lappa (Kostam)	Dehydrocostus lactone, Costunolide
19.	Trianthema portulacastrum (Saranai)	7-Hydroxy-3-methylflavone, 3,4-Dimethoxycinnamic acid, Acetyl aleuritolic acid
20.	Standard drug	Baclofen

Table No.2 The SMILES and structures of the selected phytocompounds

S.No	Phytochemical name	SMILE	Structure
1.	Protocatechuic acid	C1=CC(=C(C=C1C(=O)O)O)O	
2.	5-O-Caffeoylquinic acid	C1C(C(C(CC1(C(=O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O	

3.	Quercitrin	CC1C(C(C(C(O1)OC2=C(OC3=CC(=CC(=C3C2=O)O)O)C4=CC(=C(C=C4)O)O)O)O)O	
4.	Friedelin	CC1C(=O)CCC2C1(CCC3C2(CCC4(C3(CCC5(C4CC(CC5)(C)C)C)C)C)C)C	
5.	Rhamnetin	COC1=CC(=C2C(=C1)OC(=C(C2=O)O)C3=CC(=C(C=C3)O)O)O	
6.	Capparisinine	COC1=CC2=CC(=C1C=CC(=O)NCCCCNCCCNC(=O)C=CC3=CC(=C(C=C3)O)O2)OC	
7.	Andrographolide	CC12CCC(C(C1CCC(=C)C2CC=C3C(COC3=O)O)(C)CO)O	
8.	Neoandrographolide	CC1(CCCC2(C1CCC(=C)C2CCC3=CCOC3=O)C)COC4C(C(C(C(O4)CO)O)O)O)O	
9.	Azadirachtin	CC=C(C)C(=O)OC1CC(C2(COC3C2C14COC(C4C(C3O)(C)C56C7CC(C5(O6)C)C8(C=COC8O7)O)(C(=O)OC)O)C(=O)OC)OC(=O)C	
10.	Nimbolinin A	CC1=C2C(CC1C3=COC=C3)OC(CC4C2(C(C5C6C4(C(CC(C6(CO5)C)OC(=O)C)OC(=O)C)C)OC(=O)C7=CC=CC=C7)C)O	
11.	Piperine	C1CCN(CC1)C(=O)C=CC=CC2=CC3=C(C=C2)OCO3	

12.	Piperlongumine	COC1=CC(=CC(=C1OC)OC)C=CC(=O)N2CCC=CC2=O	
13.	Piperidine	C1CCNCC1	
14.	Pyrrolidine	C1CCNC1	
15.	Quinic acid	C1C(C(C(CC1(C(=O)O)O)O)O)O)O	
16.	Shikimic acid	C1C(C(C(C=C1C(=O)O)O)O)O	
17.	Chebulic acid	C1=C2C(=C(C(=C1O)O)O)C(C(OC2=O)C(=O)O)C(CC(=O)O)C(=O)O	
18.	Cuminaldehyde	CC(C)C1=CC=C(C=C1)C=O	
19.	p-Mentha-1,4-dien-7-al	CC(C)C1=CCC(=CC1)C=O	
20.	Alpha-Terpineol	CC1=CCC(CC1)C(C)(C)O	
21.	Eucalyptol	CC1(C2CCC(O1)(CC2)C)C	
22.	Alpha-Terpinyl acetate	CC1=CCC(CC1)C(C)(C)OC(=O)C	
23.	Beta-Amyrin	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)C)C	

24.	β-sitosterol	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C	
25.	Eugenol	COC1=C(C=CC(=C1)CC=C)O	
26.	Isoeugenol	CC=CC1=CC(=C(C=C1)O)OC	
27.	Cinnamaldehyde	C1=CC=C(C=C1)C=CC=O	
28.	Cinnamyl acetate	CC(=O)OCC=CC1=CC=CC=C1	
29.	Gingerol	CCCCCC(CC(=O)CCC1=CC(=C(C=C1)O)OC)O	
30.	Zingerone	CC(=O)CCC1=CC(=C(C=C1)O)OC	
31.	Shogaol	CCCCCC=CC(=O)CCC1=CC(=C(C=C1)O)OC	
32.	Myristicin	COC1=CC(=CC2=C1OCO2)CC=C	
33.	Elemicin	COC1=CC(=CC(=C1OC)OC)CC=C	
34.	Macelignan	CC(CC1=CC2=C(C=C1)OCO2)C(C)CC3=CC(=C(C=C3)O)OC	
35.	Sennosides	C1=CC2=C(C(=C1)OC3C(C(C(C(O3)CO)O)O)O)C(=O)C4=C(C2C5C6=C(C(=CC=C6)OC7C(C(C(C(O7)CO)O)O)O)C(=O)C8=C5C=C(C=C8O)C(=O)O)C=C(C=C4O)C(=O)O	
36.	Chrysophanol	CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=CC=C3O	

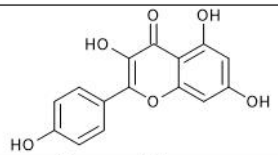
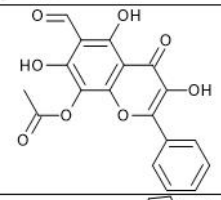
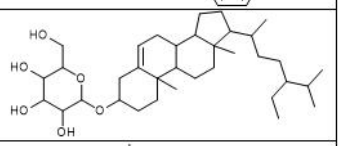
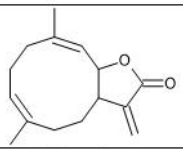
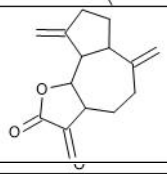
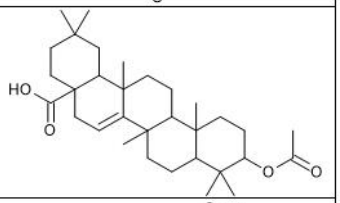
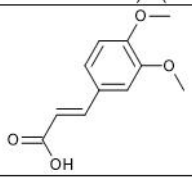
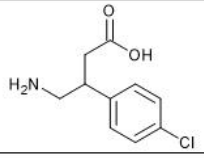
37.	Kaempferol	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O	
38.	Galangal acetate	CC(=O)OC1=C(C(=C(C2=C1OC(=C(C2=O)O)C3=CC=CC=C3)O)C=O)O	
39.	Beta-Sitosterol-d-glucoside	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)OC5C(C(C(C(O5)CO)O)O)O)O)C)C)C(C)C	
40.	Costunolide	CC1=CCCC(=CC2C(CC1)C(=C)C(=O)O2)C	
41.	Alpha-Bergamotene	CC1=CCC2CC1C2(C)CCC=C(C)C	
42.	Dehydrocostus lactone	C=C1CCC2C(C3C1CCC3=C)OC(=O)C2=C	
44.	Acetyl aleuritolic acid	CC(=O)OC1CCC2(C(C1(C)C)CCC3(C2CCC4(C3=CCC5(C4CC(CC5)(C)C)C(=O)O)C)C)C	
45.	3,4-Dimethoxycinnamic acid	COC1=C(C=C(C=C1)C=CC(=O)O)OC	
46.	Baclofen	C1=CC(=CC=C1C(CC(=O)O)CN)Cl	

Table No.3 ADME properties of the selected phytocompounds and Standard drug Baclofen

S.No	Name	Molecular weight	HBD	HBA	LogP	Lipinski violation
1.	Protocatechuic acid	154.12	3	4	1.15	0
2.	5-O-Caffeoylquinic acid	354.31	6	9	0.96	1

3.	Quercitrin	448.38	7	11	1.27	2
4.	Friedelin	426.72	0	1	4.52	1
5.	Rhamnetin	316.26	4	7	2.23	0
6.	Capparisinine	495.57	4	7	3.50	0
7.	Andrographolide	350.45	3	5	2.45	0
8.	Neoandrographolide	480.59	4	8	3.27	0
9.	Azadirachtin	720.71	3	16	3.90	2
10.	Nimbolinin A	648.74	1	10	3.67	1
11.	Piperine	285.34	0	3	3.38	0
12.	Piperlongumine	317.34	0	5	2.46	0
13.	Piperidine	85.15	1	1	1.70	0
14.	Pyrrolidine	71.12	1	1	1.51	0
15.	Quinic acid	192.17	5	6	-0.12	0
16.	Shikimic acid	174.15	4	5	0.45	0
17.	Chebulic acid	356.24	6	11	-1.0	2
18.	Cuminaldehyde	148.20	0	1	2.03	0
19.	p-Mentha-1,4-dien-7-al	150.22	0	1	2.16	0
20.	Alpha-Terpineol	154.25	1	1	2.51	0
21.	Eucalyptol	154.25	0	1	2.58	0
22.	Alpha-Terpinyl acetate	196.29	0	2	2.93	0
23.	Beta-Amyrin	426.72	1	1	4.74	1
24.	β-sitosterol	414.71	1	1	4.79	1
25.	Eugenol	164.20	1	2	2.37	0
26.	Isoeugenol	164.20	1	2	2.38	0
27.	Cinnamaldehyde	132.16	0	1	1.65	0
28.	Cinnamyl acetate	176.21	0	2	2.17	0
29.	Gingerol	294.39	2	4	3.48	0
30.	Zingerone	194.23	1	3	2.09	0
31.	Shogaol	276.37	1	3	3.28	0
32.	Myristicin	192.21	0	3	2.67	0
33.	Elemicin	208.25	0	3	2.89	0

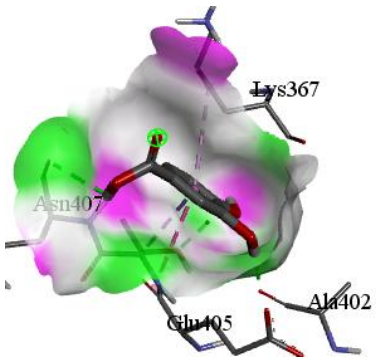
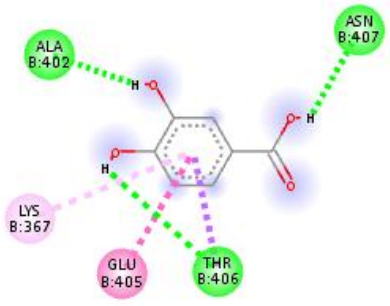
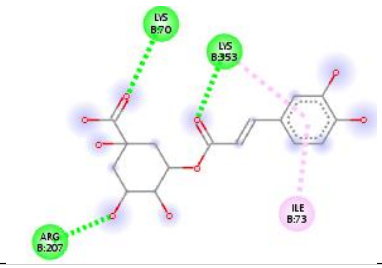
34.	Macelignan	328.40	1	4	3.27	0
35.	Sennosides	862.74	12	20	1.14	3
36.	Chrysophanol	254.24	2	4	2.22	0
37.	Kaempferol	286.24	5	6	1.70	0
38.	Galangal acetate	356.28	3	8	1.70	0
39.	Beta-Sitosterol-d-glucoside	576.85	4	6	4.98	1
40.	Costunolide	232.32	0	2	2.72	0
41.	Alpha-Bergamotene	204.35	0	0	3.41	1
42.	Dehydrocostus lactone	230.30	0	2	2.59	0
43.	7-Hydroxy-3-methylflavone	252.26	1	3	2.43	0
44.	Acetyl aleuritolic acid	498.74	1	4	3.70	1
45.	3,4-Dimethoxycinnamic acid	208.21	1	4	2.01	0
46.	Baclofen	213	2	3	1.66	0

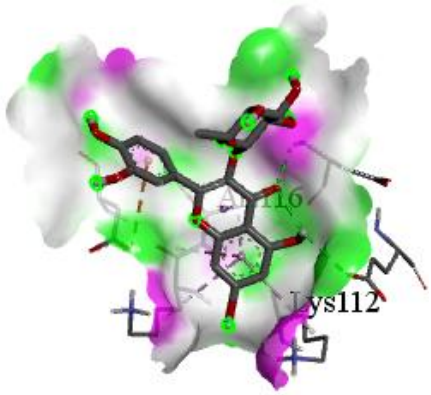
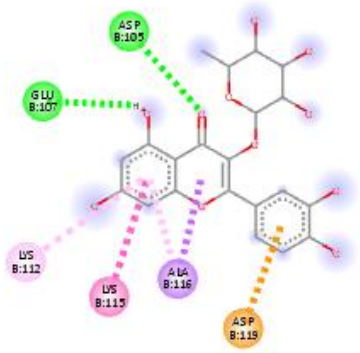
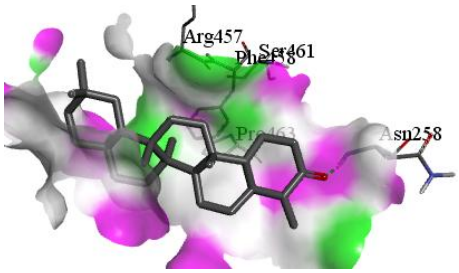
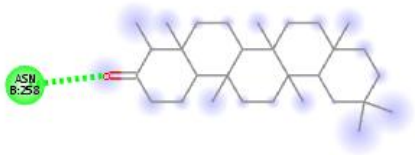
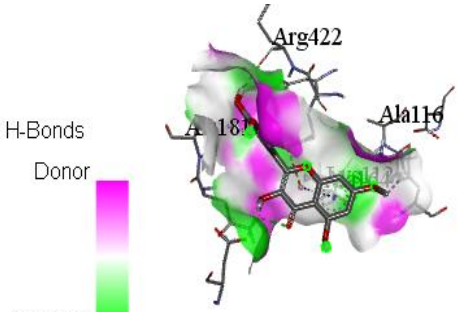
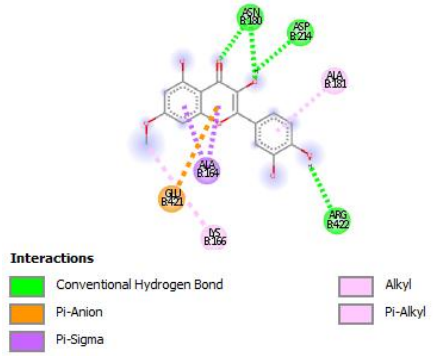
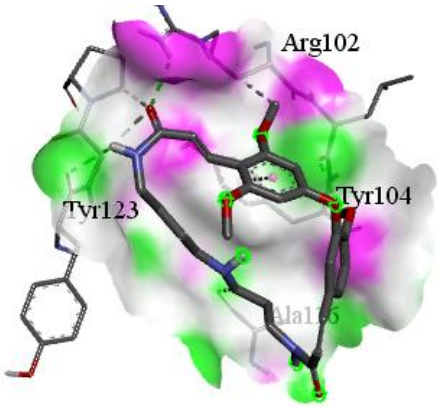
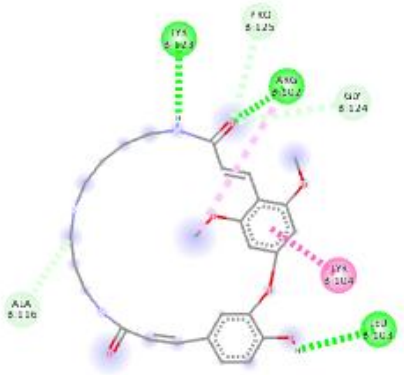
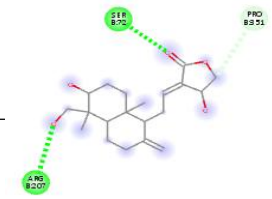
Table No.4 Molecular docking result of the selected phytocompounds and standard drugs Baclofen

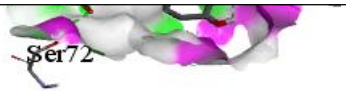
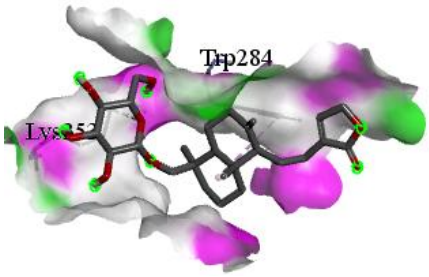
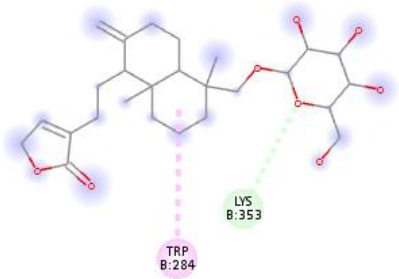
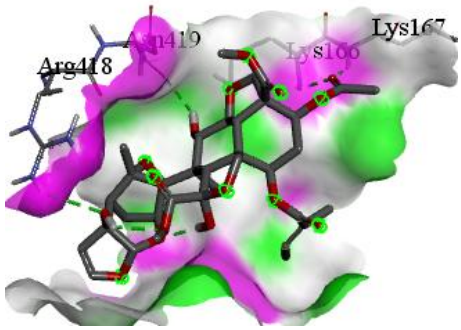
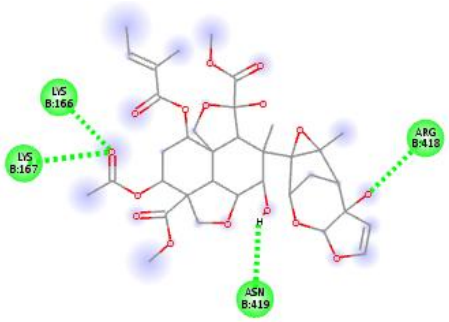
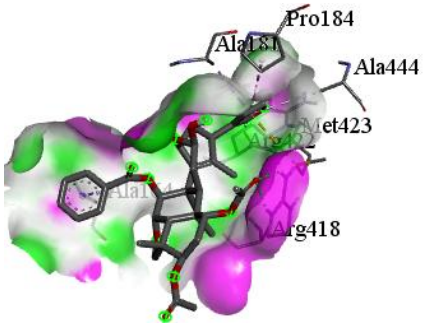
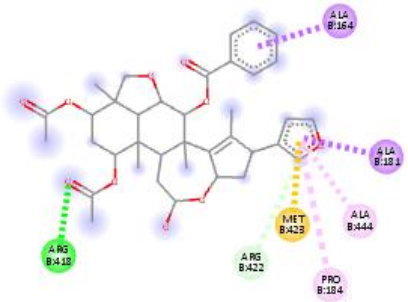
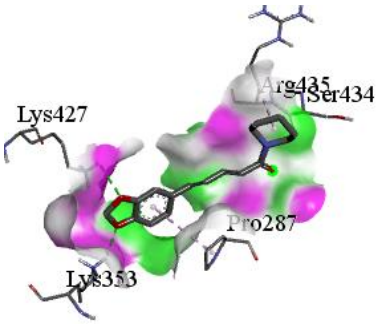
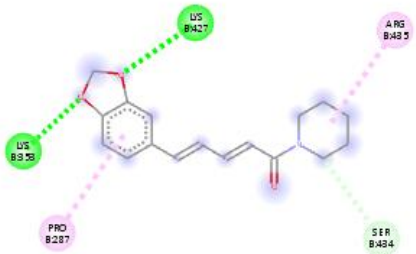
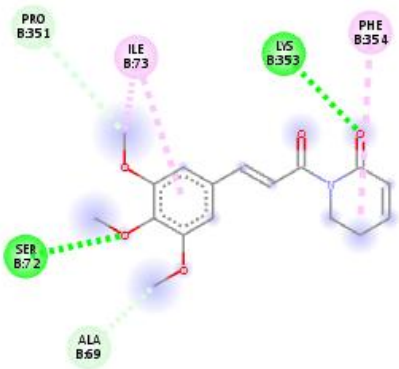
S.No	Name	Docking score
1.	Protocatechuic acid	-5.2
2.	5-O-Caffeoylquinic acid	-6.4
3.	Quercitrin	-7.0
4.	Friedelin	-8.3
5.	Rhamnetin	-6.8
6.	Capparisinine	-7.1
7.	Andrographolide	-7.5
8.	Neoandrographolide	-7.4
9.	Azadirachtin	-6.8
10.	Nimbolinin A	-8.8
11.	Piperine	-5.6
12.	Piperlongumine	-5.7
13.	Piperidine	-3.5
14.	Pyrrolidine	-2.8
15.	Quinic acid	-5.1
16.	Shikimic acid	-5.3
17.	Chebulic acid	-6.3
18.	Cuminaldehyde	-5.3
19.	p-Mentha-1,4-dien-7-al	-5.2
20.	Alpha-Terpineol	-5.1
21.	Eucalyptol	-4.7
22.	Alpha-Terpinyl acetate	-5.8
23.	Beta-Amyrin	-8.3

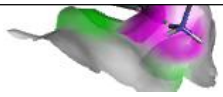
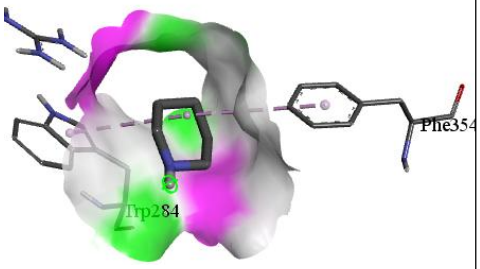
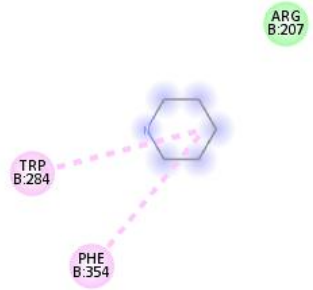
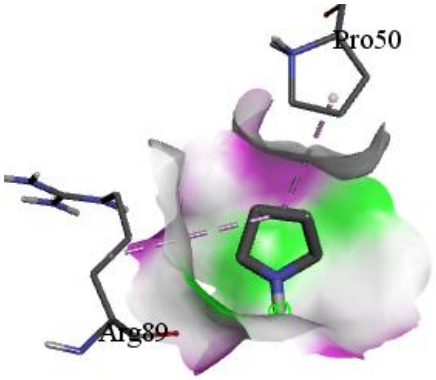
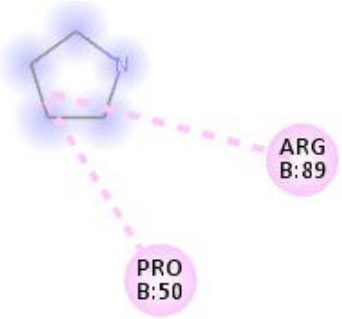
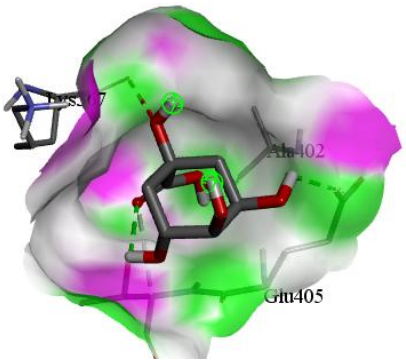
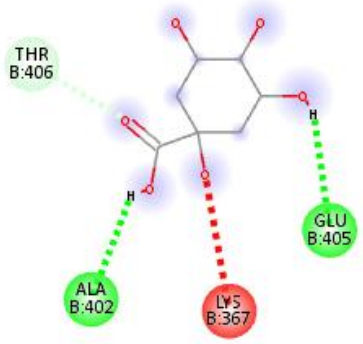
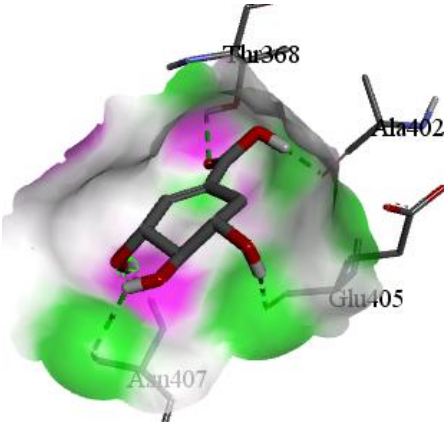
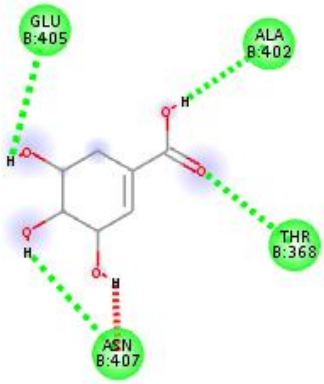
24.	β-sitosterol	-6.7
25.	Eugenol	-4.3
26.	Isoeugenol	-5.5
27.	Cinnamaldehyde	-4.5
28.	Cinnamyl acetate	-5.4
29.	Gingerol	-4.2
30.	Zingerone	-4.6
31.	Shogaol	-5.1
32.	Myristicin	-4.8
33.	Elemicin	-5.4
34.	Macelignan	-6.2
35.	Sennosides	-7.6
36.	Chrysophanol	-7.7
37.	Kaempferol	-7.4
38.	Galangal acetate	-6.7
39.	Beta-Sitosterol-d-glucoside	-7.2
40.	Costunolide	-6.5
41.	Alpha-Bergamotene	-6.3
42.	Dehydrocostus lactone	-6.4
43.	7-Hydroxy-3-methylflavone	-7.2
44.	Acetyl aleuritolic acid	-6.9
45.	3,4-Dimethoxycinnamic acid	-4.9
46.	Baclofen	-5.4

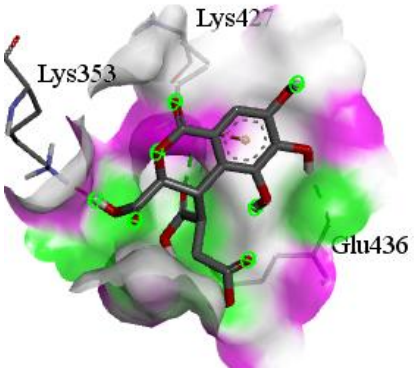
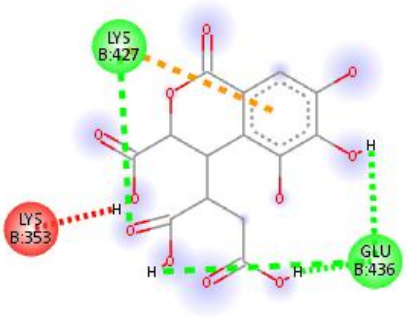
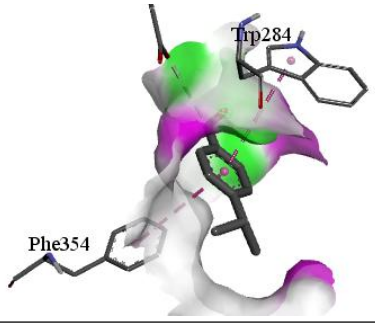
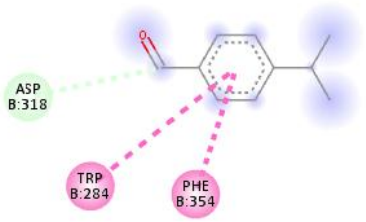
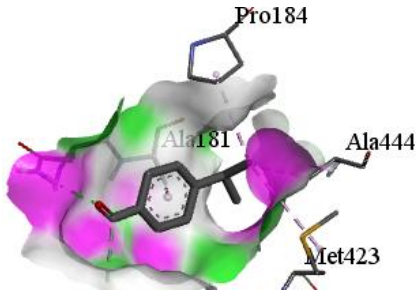
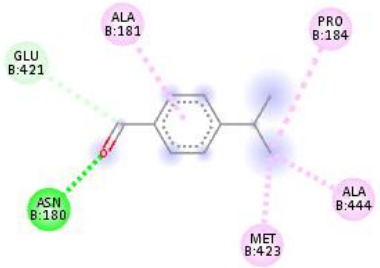
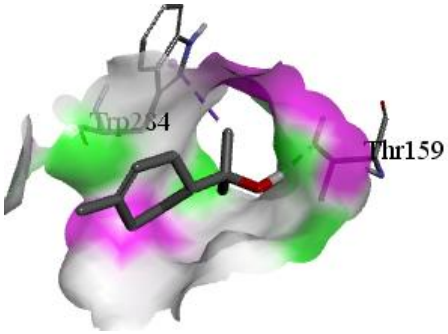
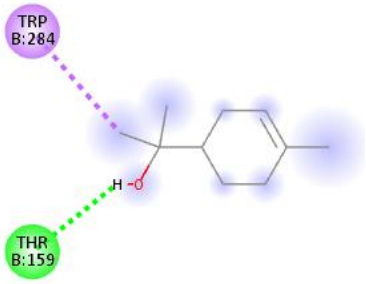
Table No.5 3D and 2D interaction of phytocompound with GABA receptor protein

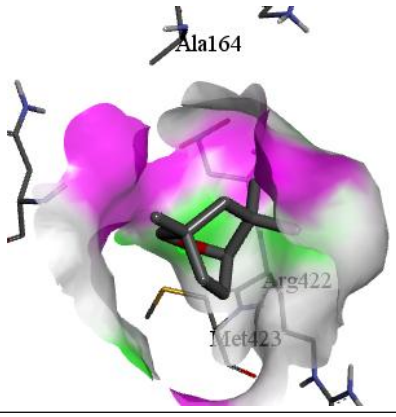
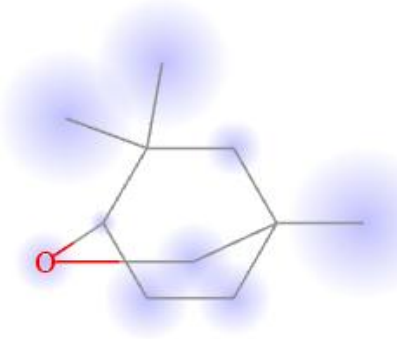
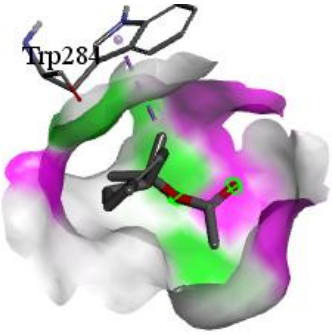
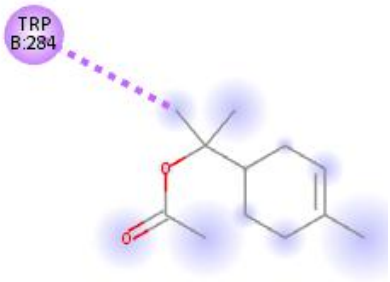
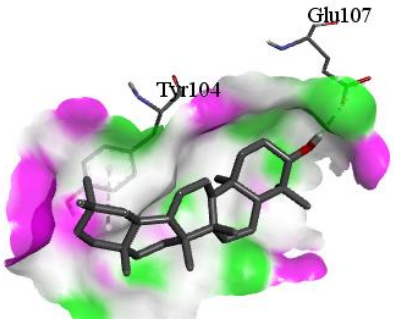
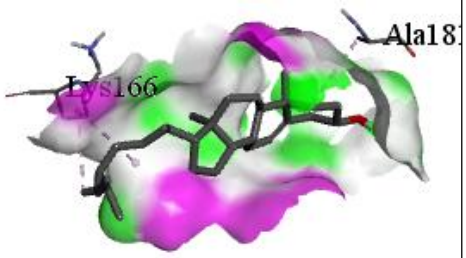
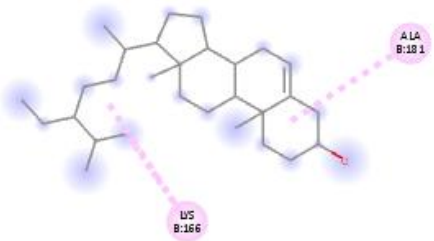
Phytochemical Name	2D interaction	3D interaction
Protocatechuic acid		
5-O-Caffeoylquinic acid		

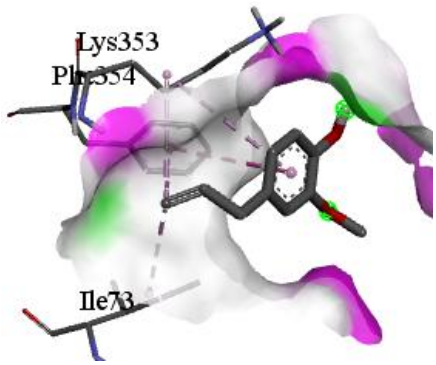
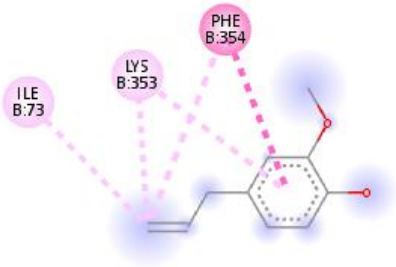
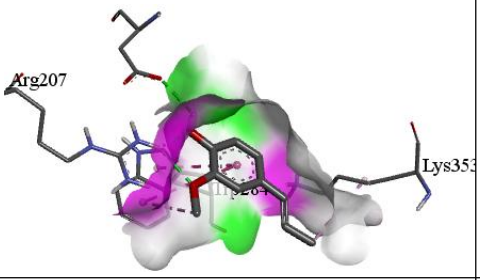
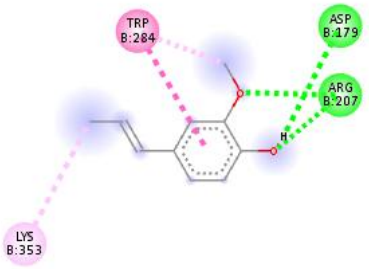
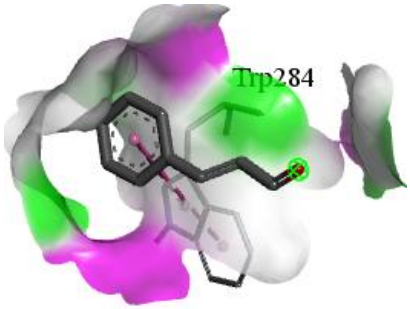
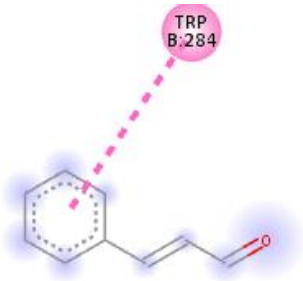
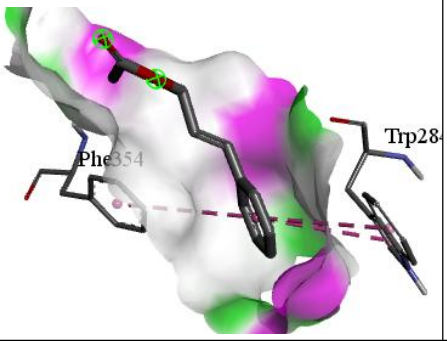
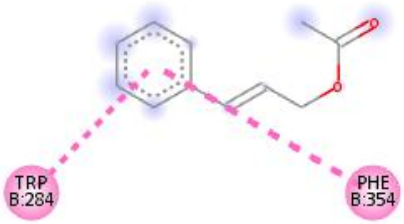
Quercitrin		
Friedelin		
Rhamnetin		
Capparisinine		
Andrographolide		

		
Neoandrographolide		
Azadirachtin		
Nimbolinin A		
Piperine		
Piperlongumine		

		
Piperidine		
Pyrrolidine		
Quinic acid		
Shikimic acid		

Chebulic acid		
Cuminaldehyde		
p-Mentha-1,4-dien-7-al		
Alpha-Terpineol		

Eucalyptol		
Alpha-Terpinyl acetate		
Beta-Amyrin		
β-sitosterol		

Eugenol		
Isoeugenol		
Cinnamaldehyde		
Cinnamyl acetate		
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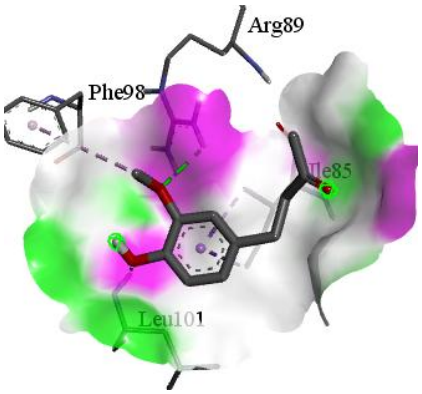
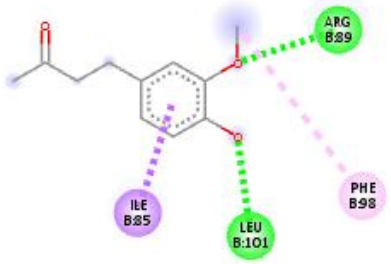
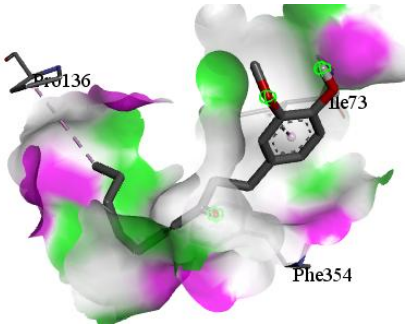
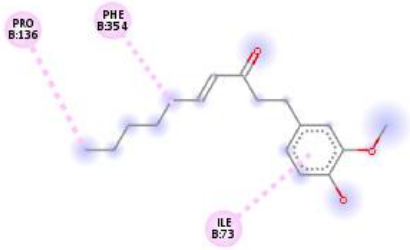
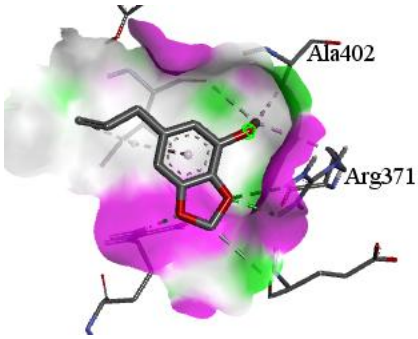
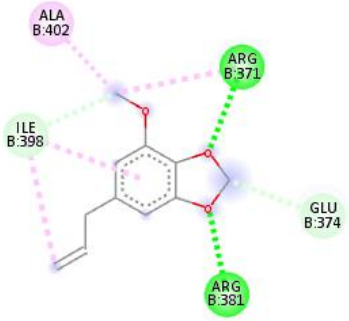
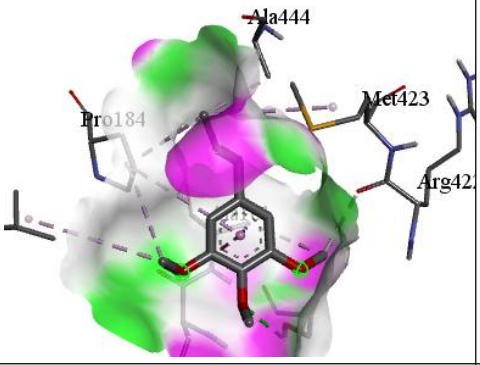
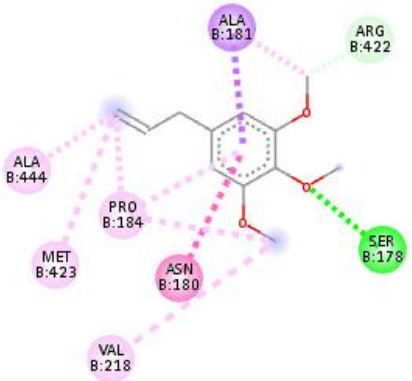
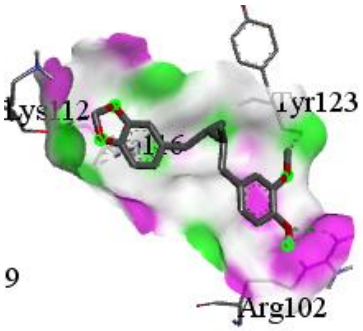
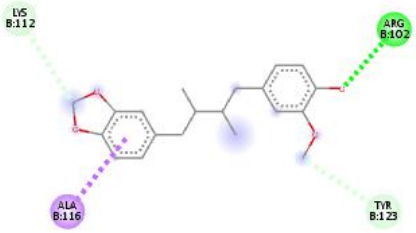
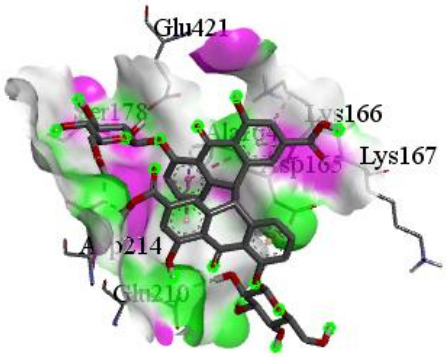
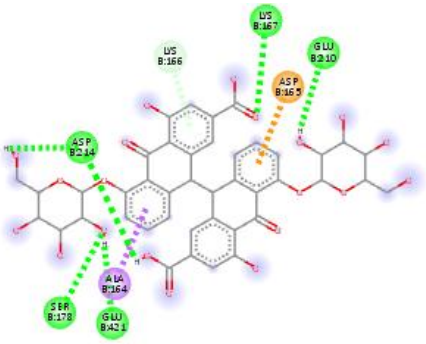
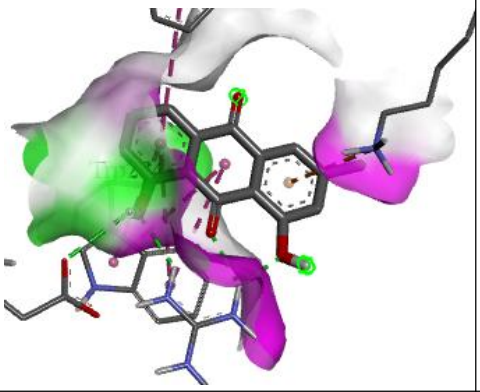
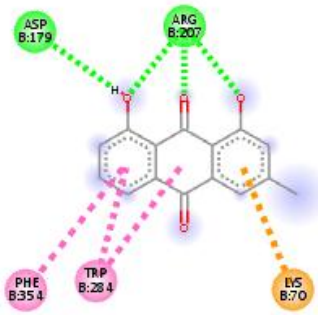
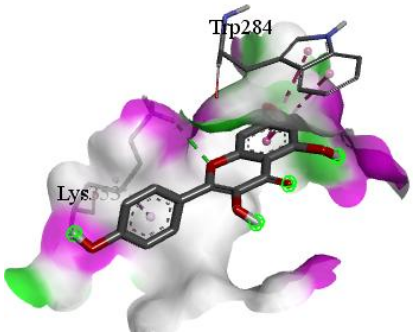
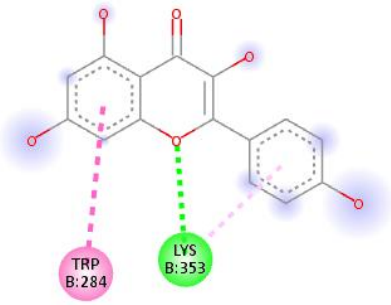
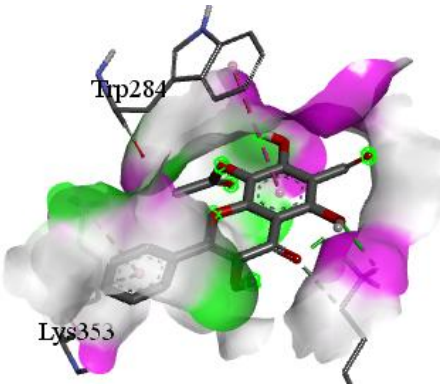
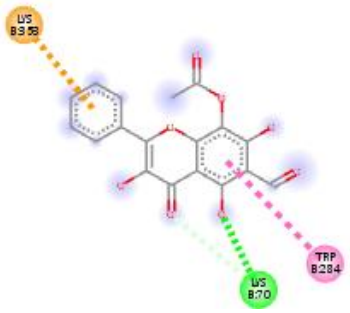
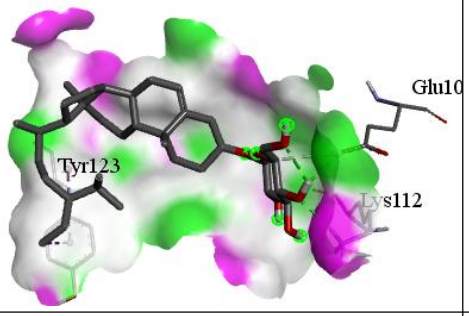
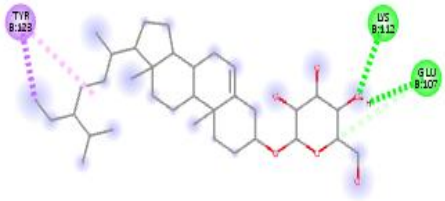
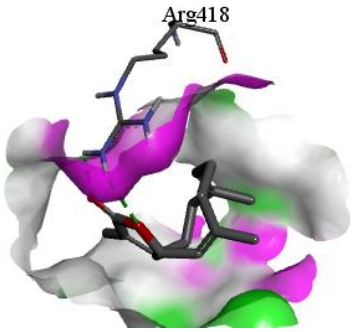
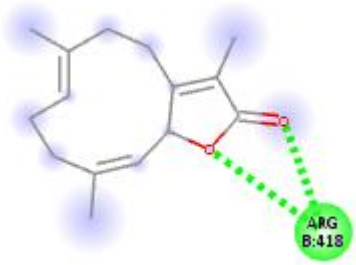
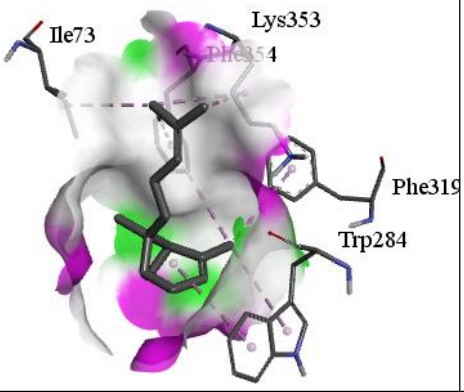
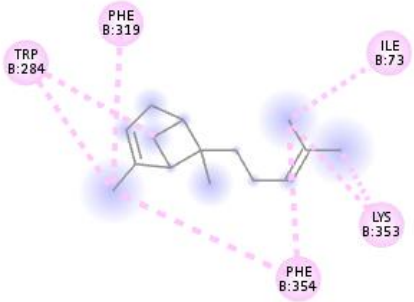
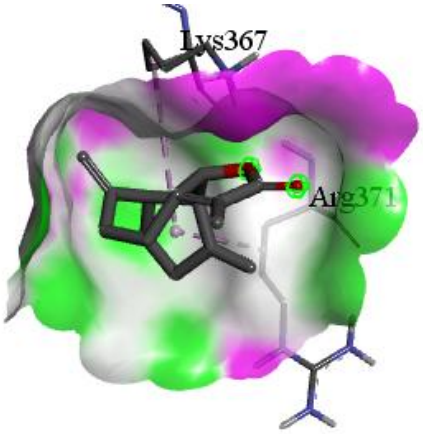
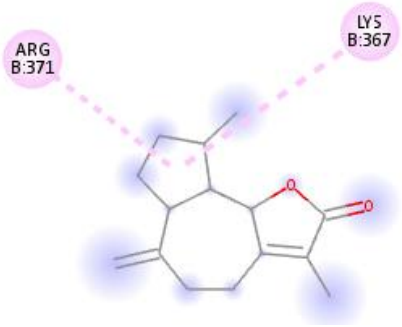
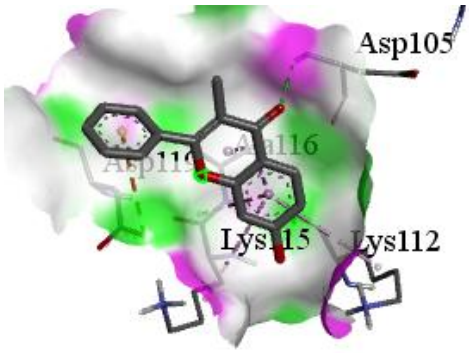
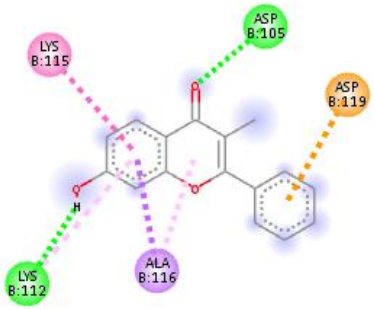
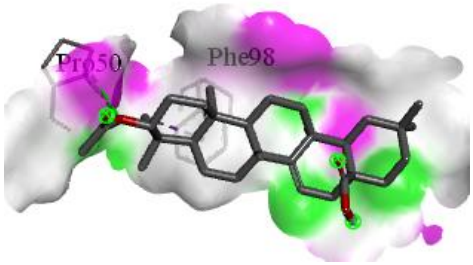
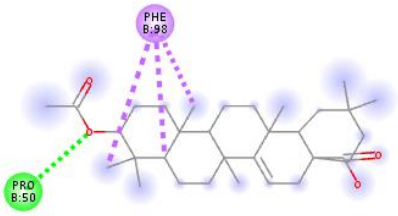
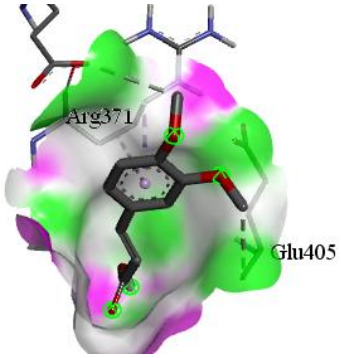
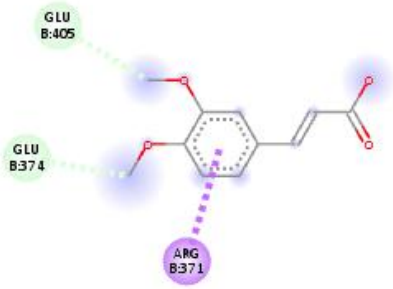
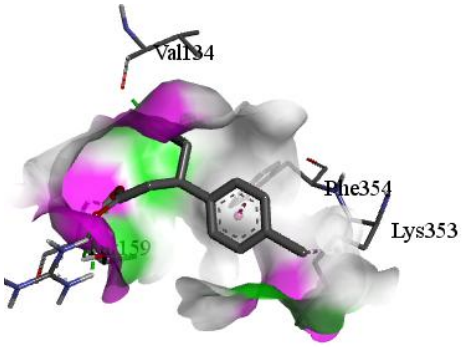
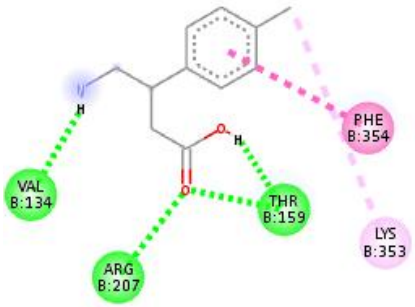
Zingerone		
Shogaol		
Myristicin		
Elemicin		

Macelignan		
Sennosides		
Chrysophanol		
Kaempferol		

Galangal acetate		
Beta-Sitosterol-d-glucoside		
Costunolide		
Alpha-Bergamotene		

Dehydrocostus lactone		
7-Hydroxy-3-methylflavone		
Acetyl aleuritolic acid		
3,4-Dimethoxycinnamic acid		

Baclofen		

Results and discussion:

ADME and Toxicity study:

Based on the result of SWISSADME, the number of phyto compounds and standard drug Baclofen had no violation of Lipinski rule of five. Out of forty six compounds 34 phytochemicals had no Lipinski violation, 8 phytochemical had one violation, 3 phytochemical had two violations and one phytochemical had three violations. The high docking score (more than -8.0 kcal/mol) phyto compounds like Friedelin, Nimbolinin A and Beta-Amyrin had one Lipinski violation. The high docking score (more than -7.0 kcal/mol) phyto compounds like Capparisinine, Andrographolide, Neoandrographolide, Chrysophanol and 7-Hydroxy-3-methylflavone had no Lipinski violation.

Interpretation of Molecular docking study:

From the molecular docking study three compounds had docking score more than -8.0 kcal/mol, nine compounds had -7 to -8 kcal/mol, eleven compounds had -6 to -7 kcal/mol and fourteen compounds had -5 to -6 kcal/mol with the GABA receptor protein. The standard drug Baclofen had three hydrogen bond interactions with VAL B:134, ARG B:207, THR B:159 Pi-alkyl interaction with PHE B:354 and LYS B:353 amino acids of GABA receptor protein with a docking score of -5.4 kcal/mol. The Beta-Amyrin had one hydrogen bond interaction with GLU B:107 and Pi-alkyl interaction with TYR B:104 amino acids of GABA receptor protein with a docking score of -8.3 kcal/mol. The Friedelin had one hydrogen bond interaction with ASN B:418 amino acids of GABA receptor protein with a docking score of -8.3 kcal/mol. The Nimbolinin A had two hydrogen bond interactions with ARG A:258 and ARG B:422, Pi-sigma interaction with ALA B:164 and ALA B:181, Pi-alkyl interaction with ALA B:144 and PRO B:184 amino acids of GABA receptor protein with a docking score of -8.8 kcal/mol.

The Quercitrin had three hydrogen bond interactions with ARG B:207, LYS B:70 and LYS B:353 and Pi-alkyl interaction with ILE B: 73 amino acids of GABA receptor protein with a docking score of -8.3 kcal/mol. The Capparisinine had the hydrogen bond interaction with LEU B:103, ARG B:102, TYR B:123, PRO B:125, GLY B:124, ALA B:116 and Pi-Pi stacked interaction with TYR B:104 amino acids of GABA receptor protein with a docking score of -7.1 kcal/mol. The Beta-Sitosterol-d-glucoside had two hydrogen bond interactions with LYS B:112, GLUB:207 Pi-Sigma interaction with TYR B:123 amino acids of GABA receptor protein with a docking score of -7.2 kcal/mol. The 7-Hydroxy-3-methylflavone had two hydrogen bond interaction with LYS B:112, ASP B:105, Pi-anion interaction with ASP B:119, Amid-Pi stacked interaction with ASP B:119 and Pi-Sigma interaction with ALA B:116 amino acids of GABA receptor protein with a docking score of -7.2 kcal/mol.

Conclusions:

Based on the results of the molecular docking study with the GABA receptor protein, several compounds exhibited promising docking scores and interactions: **Nimbolinin A**: Demonstrated the highest docking score (-8.8 kcal/mol) with multiple hydrogen bond interactions and Pi interactions with various amino acids of the GABA receptor protein. **Beta-Amyrin and Friedelin**: Both showed high docking scores (-8.3 kcal/mol) with significant hydrogen bond interactions, indicating potential affinity for the GABA receptor protein. **Quercitrin:** Exhibited a docking score of -8.3 kcal/mol with multiple hydrogen bond interactions and Pi-alkyl interaction, suggesting strong binding potential. **Capparisinine**: Showed moderate docking score (-7.1 kcal/mol) but with multiple hydrogen bond interactions and Pi-Pi stacked interaction, indicating favorable binding characteristics. **Beta-Sitosterol-d-glucoside and 7-Hydroxy-3-methylflavone**: Both demonstrated reasonable docking scores (-7.2 kcal/mol) with significant hydrogen bond interactions and other molecular interactions. Based on our in silico study of Parangipattai Kasayam, we have found compelling evidence that its bioactive compounds possess notable binding affinity for GABA receptors. This discovery suggests that Parangipattai Kasayam may effectively enhance muscle relaxation through its interaction with these receptors, thereby potentially aiding in the management of spasticity in children with cerebral palsy. The GABA receptors are integral in regulating muscle tone and movement by inhibiting neural activity in the central nervous system. In cerebral palsy, where there is often heightened muscle stiffness and involuntary contractions (spasticity), enhancing GABAergic activity could alleviate

these symptoms. The strong binding affinity observed between Parangipattai Kasayam compounds and GABA receptors provides a scientific basis for its traditional use in managing spasticity. By supporting GABA receptor function, this herbal medicine could offer a promising avenue for developing novel treatments or complementary therapies for cerebral palsy. Further research, including experimental studies both in the lab and in clinical settings, is essential to corroborate these findings and to establish the safety, efficacy, and optimal application of Parangipattai Kasayam in managing spasticity associated with cerebral palsy.

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