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Research article

In silico analysis of green tea catechins for design of adenosine A2A antagonist and nav 1.7 inhibitors

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ABSTRACT

Neuropathic pain is a sensory nerve system disorder that affects a large percentage of the world's elderly population. A sensory nerve system injury causes it, which can lead to function loss, acute discomfort, and heightened pain sensitivity. The PNS is in responsible of the start and maintenance of Neuropathic Pain, despite the fact that the CNS is the major controller of pain. Diseases like diabetes and cancer are connected to a change in lifestyle in today's globe. Concentrating compounds that can boost neurotransmitter release can be used to treat these disorders. Adenosine receptors and sodium channels are the next targets for inflammatory and peripheral neurological diseases.Green tea contains antioxidants such as catechins, EC, EGC, ECG, EGCG, GC, CG, GCG, GCG3ME, ECG3Me, EGCG3Me, and EGCG4Me. This research describes how molecular docking and virtual screening were used to assess the binding potential of green tea catechins for human adenosine A2A receptors and sodium channel Nav 1.7 inhibitors. As a result, a number of Green Tea Catechins exhibit exceptional binding abilities.

Keywords: Green Tea Catechins, Adenosine A2A, Nav 1.7, Molecular Docking, Virtual Screening

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INTRODUCTION

Pain is an apprehensive sensation caused by an acute and injurious trigger that can be either acute or chronic depending on the length of time. Neuropathic pain is typically chronic, lasting for months or years and characterized by recurrent painful episodes [1,2]. Pain induced by a lesion or disease affecting the somatosensory system is described as "pain caused by a lesion or disease affecting the somatosensory system" [3] and can result in both loss of function and disability. Neuropathic pain affects roughly 7-10% of the general population, according to [4]. Neuropathic pain differs from nociceptive pain, which is described as "pain that results from actual or threatened harm to non-neural tissue and is caused by nociceptor activation" [5].

The somatosensory nerve system is functionally normal in nociceptive pain, with aberrant function underlying neuropathic pain. It is prevalent in cancer patients, and it occurs as a result of direct damage to the neurological system caused by a primary tumour or metastases, or as a result of cancer treatment, such as chemotherapy [6]. According to 20% of cancer pain is solely neuropathic in origin. Neuropathic pain was linked to more oncological treatment, higher analgesic requirements (including powerful opioids and adjuvant analgesics), and lower performance status than nociceptive pain, according to a 2012 study [7]. Patients with neuropathic pain also reported poor physical, cognitive, and social functioning.

Adenosine is the primary neuromodulator in the brain, acting as a supporter for neurotransmitters. Adenosine receptors are a G-protein coupled receptor family that includes four members: A1, A2A, and A3 receptors. They are found in practically every human body tissue and organ. In terms of the molecular pathways and second messengers involved, the A1 and A3 receptors inhibit adenyl cyclase (AC) through the G-protein, whereas the A2A and A2B receptors stimulate it through the Gs protein. Adenosine also plays a role in the inflammation process by causing the production of TNF-a, macrophage inflammatory protein (MIP)-1a, MIP-1b, MIP-2a, and M. Adenosine and adenosine receptor agonists exhibit antinociceptive effects in animal models of acute [8], inflammatory [9] Dopamine and adenosine. In excitable cells, such as nerve, muscle, and neuroendocrine cells, voltage-gated sodium channels are responsible for action potential initiation and propagation [10,11]. Because of their role in neuropathic pain, sodium

channels such as Nav 1.3, Nav 1.7, Nav 1.8, and Nav 1.9 are of interest for therapeutic development. Nav1.7 is a voltage-gated sodium channel that is vital for electrical signalling in most excitable cells.

Figure 1: Protein Structure of human adenosine receptor A2A (PDB ID 2YDV)

Figure 2: Protein Structure of Nav 1.7 receptor (PDB ID 5EK0)

It plays a key role in the generation and conduction of action potentials. Nav1.7 is found near the ends of pain-sensing nerves, known as nociceptors, which are located close to the point where the impulse is triggered. The Nav1.7 channel amplifies these membrane depolarisations and the neuron fires when the membrane potential difference reaches a certain threshold. Multiple voltage-dependent sodium currents in sensory neurons can be distinguished based on their voltage dependency and susceptibility to the voltage-gated sodium-channel blocker tetrodotoxin [12, 13]. The Nav1.7 channel produces a rapidly activating and inactivating current that is responsive to the amount of tetrodotoxin. In the early stages of neuronal electrogenesis, Nav1.7 is critical. When the channel is depolarized, even to a slight degree, Nav1.7 activity occurs, which is defined as a gradual transition of the channel toward an inactive state [14]. This characteristic allows these channels to stay available for activation even when depolarizations are minor or slow to develop. The stimulation of nociceptor nerve endings causes "generator potentials," or tiny voltage changes across the neuronal membranes [15].

MATERIALS AND METHODS

Molecular Docking

The selection criteria for a satisfactory resolution are indicated by the B factor, which refers to the thermostability of the protein structures of human adenosine receptor A2A with NECA bound (N-ethyl-50-carboxamido-PDB ID 2YDV) [16] and Human Nav 1.7-VSD4-NavAb with GX-936 bound (PDB ID 5EK0) [17] generated from the free Protein database www.rcsb.org.

Figure 3: Binding Site of Adenosine A2A Receptor

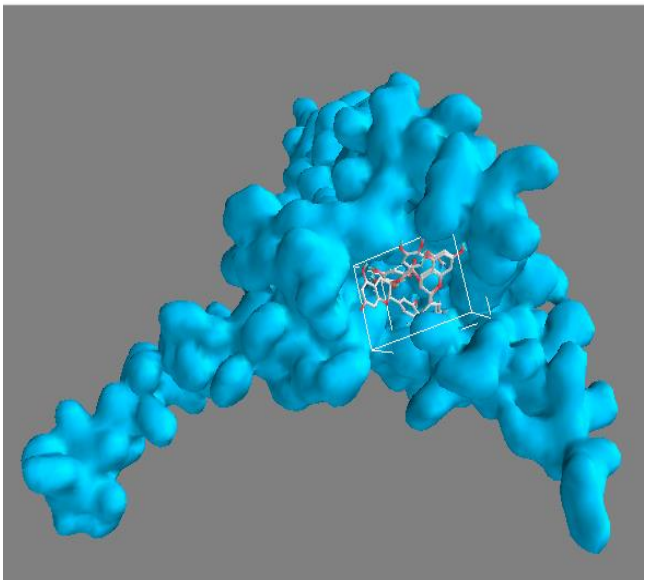


Figure 4: Binding Site OfNav1.7 Receptor

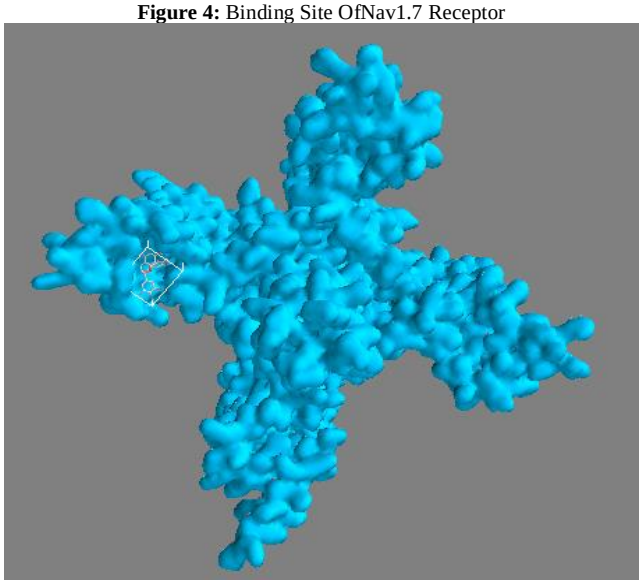
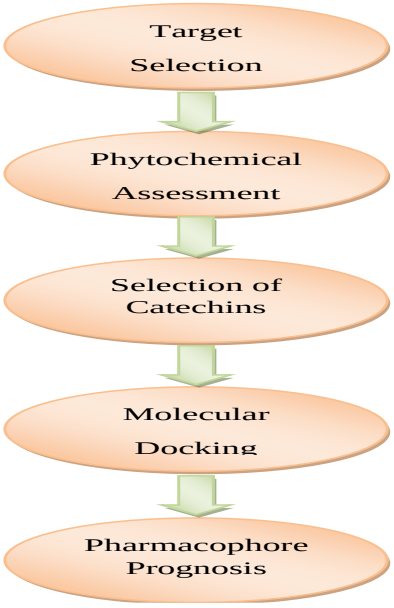


Figure 5: Overview of the applied computational methodology



The atomic resolution of chosen PDBs was validated using the X-Ray Diffraction technique. 2YDV and 5EK0 have atomic resolutions of 2.6 and 3.53, respectively, with R values free of 0.258 and 0.272. All of the PDBs 2YDV and 5EK0 that were chosen for docking studies passed all of the validation parameters. The structural estimation of Human adenosine receptor A2A and Human Nav 1.7-VSD4-NavAb was accomplished using Biovia Discovery Studio Visualizer. The Ligand Binding Sites of Human Adenosine Receptor A2A and Nav 1.7-VSD4-NavAb are shown in Figures 3 and 4.

Table No 1: List of Catechins present in Green Tea

Name of the Catechins
Epicatechin (EC
Epigallocatechin (EGC)
Epicatechin Gallate (ECG)
Epigallocatechin Gallate (EGCG)
Catechin (C)
Gallocatechin (GC)
Catechin-3-O-Gallate (CG)
Gallocatechin-3-O-Gallate (GCG)
Epigallocatechin-3-O-(3-O-Methyl) Gallate (EGCG3” Me)
Gallocatechin-3-O-(3-O-Methyl) Gallate (GCG3” Me)
Epigallocatechin-3-O-(4-O-Methyl) Gallate (EGCG4” Me)
Epicatechin-3-O-(3-O-Methyl) Gallate (ECG3” Me)

By shifting water molecules and adding polar hydrogen atoms, protein clarity is required to secure the native shape of the adenosine A2A receptor and native ligands of Nav 1.7-VSD4-NavAb. Native ligands were removed since they could interfere with docking induction. Table no.1 shows the ligand structures of several catechins compounds [18]. Catechins compound structures were designed and transferred to the Mol-2format, then optimised using Biovia Discovery Studio Visualizer and molecular mechanics calculations with the use of MMFF. Redocking was done with GX-936 and Human Nav1.7 prior to docking activation. The docking activations were replicated with a root mean square deviation (RMSD) of less than 1.0 [19]. The activation of GRIP docking is done by of docking, a versatile protein-ligand docking approach. The rotation angle between two forms was preserved at 10° during docking activation, and the total number of rotations was set to 30 [20]. The best docking position for each molecule was chosen based on its binding energy and the amount of connections it has, such as hydrogen bond contacts, aromatic interactions, charge interactions, and the complex's binding energy. Figureure-5 depicts an overview of the computational methods used

ADME Prognosis

The information about rotatable bonds, hydrogen acceptor/donor bonds, GI absorption, and BBB permeability is described in the ADME, which includes drug-likeness analysis [21,22,23,24] this can be created with the help of the Swiss ADME web site. In order to forecast variables that may modify pharmacokinetics bearing on selected phytochemical structures, in silico pharmacokinetic research is conducted [25]. The ADME web portal was created by the Swiss Institute of Bioinformatics and is used to calculate physicochemical attributes as well as forecast ADME parameters and drug like nature [26].

Pharmacophore Prognosis

Pharmacophores are a group of qualities that are required for biological activity. The Zinc Pharmer Free Database was used to create pharmacophores for the selected Catechins, which are important in binding to the human adenosine receptor A2A and Nav 1.7-VSD4-NavAb.For the pharmacophore prognosis of human adenosine receptor A2A and Nav 1.7-VSD4-NavAb, the structures of NECA and GX-936 were employed as references, respectively. The lowest feature threshold in pharmacophore prognosis was preserved at 3 and the maximum at 5.

RESULT AND DISCUSSION

Effective Screening and Molecular Docking Studies

Protein structures of Human adenosine receptor A2A and Human Nav1.7-VSD4-NavAbin complex with NECA and GX-936 [17] were retrieved from the free protein database www.rcsb.org for molecular docking vitalization. To begin to reap the benefits of the docking convention, NECA and GX-936 were redocked and the RMSD was determined. The RMSD between co-crystallized NECA, GX-936, and docked posture was found to be 0.76Å and 0.82Å, indicating that the docking convention used was capable of synthesising binding conformations that were close to experimentally discovered interactions.

Six catechins were discovered to be interacting with human adenosineA2A and Nav 1.7 receptors in stable conformation after a detailed examination of the binding interaction and binding energy of selected 12 Catechins. The docking score of Epigallocatechin gallate

(EGCG) with Adenosine A2A and Nav 1.7 receptors was reported to be -8.3 and -8.2, respectively. EGCG was discovered to interact with ARG102, ASN42 via a traditional hydrogen bond, with THR41 via a Pi-sigma interaction, and with LEA292, ALA105, LYS227 via a Pi-alkyl interaction. Figure 6 shows Vander Wal's interaction with the Adenosine A2A receptor's ASN113, TYR112, PRO109, LEA108, GLU228, ILE106, ALA231, HIS230, TYR288, PHE295, VAL45, LEU37, and ASN39.EGCG was discovered to interact with SER1635, PRO1631, ASN1714 via a traditional hydrogen bond, with VAL721, ALA1625 via a Pi-sigma interaction, and with ALA1723, ALA1718, LEU1626 via a Pi-Alkyl interaction. Figure 12 shows Vander Wal's interaction with the Nav.7 receptor's ASP1722, GLY1632, LEU1634, MET1633, ILE1622, VAL1636, VAL1629, VAL177, ILE1719, ILE1726.

Catechin has a docking score of -8.8 and -9.4, respectively, with the Adenosine A2A and Nav 1.7 receptors. Catechin was discovered to interact with ILE66, GLU169, and THR88 via a conventional hydrogen bond, ILE274 via a Pi-sigma interaction, VAL84 via a Pi-alkyl interaction, and PHE168 via a Pi-Pi stacking interaction. Figure 7 shows Vander Wal's interaction with the Adenosine A2A receptor's LEU167, MET270, LEU249, LEU85, TRP246, HIS278, SER277, ALA63, and SER67. Catechin was discovered to interact with TYR1537 via a traditional hydrogen bond, with ASP586 via a Pi-anion interaction, with ARG1605, ARG1602 via a Pi-alkyl interaction, and with ALA1585 via a Pi-Pistacked interaction. In Figure.13, Vander Wal interacts with the Nav1.7 receptor's ALA1604, ILE1601, GLY1581, PHE1598, GLU1589, MET1582, VAL1541, ASN140, ILE1544.

The docking score of Catechin-3-O-gallate (CG) with Adenosine A2A and Nav 1.7 receptors was reported to be -9.9 and -9.4, respectively. CG was discovered to interact with ALA63, TYR9, PHE168, HIS264 via a traditional hydrogen bond, with GLU169 via a Pi-anion interaction, with MET270, LEU267 via a Pi-alkyl interaction, and with LEU249, ILE274 via a Pi-sigma interaction. The interaction of Vander Wal with the Adenosine A2A receptor ILE64, HIS278, ASN253, MET177, TRP246, LEU85, ILE66, ASP170, LEU167, SER67, TYR271, ALA265 is illustrated in Figure. 8. CG was discovered to interact with VAL1593, GLU1594 via a normal Hydrogen bond, with GLU1657, GLU1589 via a Pi-anion interaction, with PRO1595 via a Pi-alkyl interaction, and with SER1594 via a Pi-alkyl interaction with SER1594 by formation of Amide Pi-stacked interaction. The interaction of Vander Wal with the Nav 1.7 receptor PHE1598, GLN1528, TYR1537, ARG1602, GLU1524, GLN1653, THR1652, LYS1525, GLU1526, GLY1656, THR1533, PHE1588 is depicted in Figure.14.

The docking score of gallocatechin-3-O-gallate (GCG) with Adenosine A2A and Nav 1.7 receptors was determined to be -9.6 and -9.4, respectively. GCG was discovered to create Conventional Hydrogen Bonds with ASN253, SER67, HIS264, ALA25, LEU249, LEU167 via development of Pi-alkyl interaction, ILE24, LEU267 by formation of Pi-sigma interaction, and PHE168 by formation of Pi-Pi interaction. The interaction of Vander Wal with the Adenosine A2A receptor TYR271, GLU169, THR68, GLY5, ILE3, VAL84, ILE66, ALA63, MET270, PRO266 is depicted in Figure.9. GCG was discovered to interact with ILE1588 via a Conventional Hydrogen Bond, with GLU1657, GLU1589 via a Pi-anion interaction, with PRO1595 via a Pi-alkyl contact, and with SER1594 via an Amide Pi-stacked interaction. In Figure.15, Vander Wal interacts with the Nav 1.7 receptors TYR1537, ARG1602, GLU1524, GLN1653, THR1652, LYS1525, GLU1656, THR1533, GLN1530, PHE1598, PHE1592, VAL1593.

The docking score of Epigallocatechin-3-O-(3-O-methyl) gallate (EGCG3” Me) with Adenosine A2A and Nav 1.7 receptors was determined to be -7.5 and -8.3, respectively. EGCG3” Me was discovered to engage with ALA3 via a Conventional Hydrogen Bond, with GLU169 via a Pi-anion interaction, with LEU267, ILE3, and LEU167 via a Pi-alkyl contact, and with ILE274 via a Pi-sigma interaction. Figure 10 shows Vander Wal's interaction with the Adenosine A2A receptor's TYR9, TYR271, SER67, PHE18, MET270, ASP170, HIS264, and LYS153. EGCG3” Me was discovered to interact with ASP1571, ARG1554, GLU1558 by forming a Conventional Hydrogen Bond, with GLU1582 by forming a Pi-anion interaction, with ALA1615 by forming a Pi-alkyl interaction, and with THR1507 by forming a Pi-sigma interaction, with ASP1571, ARG1554, GLU1558 by forming a Conventional Hydrogen Bond, with GLU1582. The interaction of Vander Wal with the Nav 1.7 receptor TRP1567, PHE1506, VAL1501, PHE152, SER1568, ASP1568, SER1503, SER1504, ILE1510, PRO1617, ARG1611, ILE1514, ARG1620 is depicted in Figure.16.

The docking score of Epicatechin-3-O-(3-O-methyl) gallate (ECG3” Me) with Adenosine A2A and Nav 1.7 receptors was reported to be -8.4 and -8.3, respectively. ECG3” Me was discovered to interact with ASN39, TYR288 via a Conventional Hydrogen Bond, and with TYR112, ALA105, ILE292 via a Pi-alkyl interaction. Figure 11 shows Vander Wal's interaction with the Adenosine A2A receptor's ASN42, THR41, ASN36, GLU294, ASN113, SER234, ALA231, HIS230, and LYS227. By forming a Conventional Hydrogen Bond with ARG1620, ASP1571, ARG1554, SER1568, ASP1565, ECG3” Me was discovered to interact with ARG1620, ASP1571, ARG1554, SER1568, ASP1565, GLU1502 by forming a Pi-cation contact, ALA1615 by forming a Pi-alkyl interaction, and HIS1558 by forming a Pi-alky stacked interaction. In

Figure.17, Vander Wal interacts with the Nav 1.7 receptors ILE1510, GLU1550, PHE1506, THR1507, SER1504, SER1503, VAL1501, PHE1562, ARG1611, TRP1567, THR1614.

Figure 6: Binding interaction of epigallocatechin gallate with human adenosine receptor A2A (Generated using Free Version of Discovery Studio Visualizer)

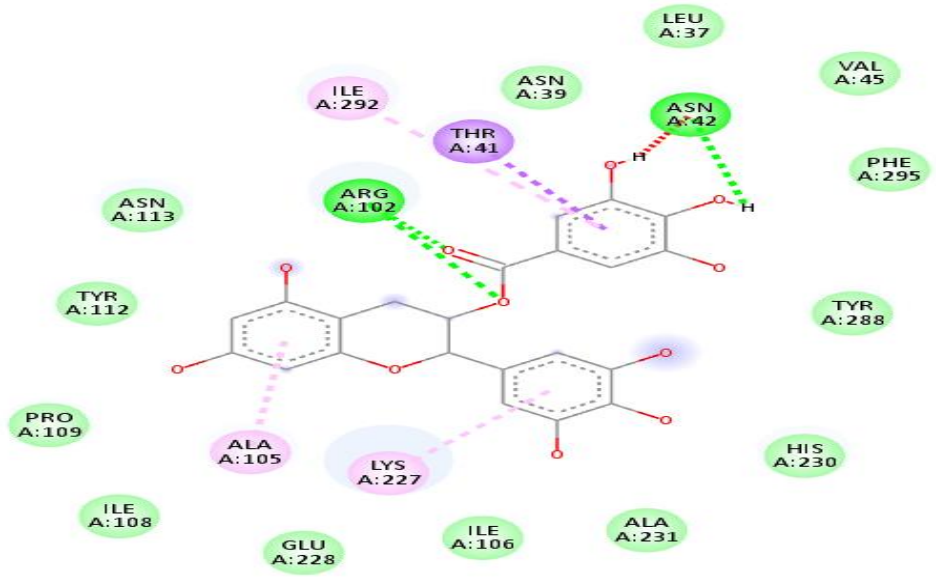


Figure 7: Binding interaction of Catechin with human adenosine receptor A2A (Generated using Free Version of Discovery Studio Visualizer)

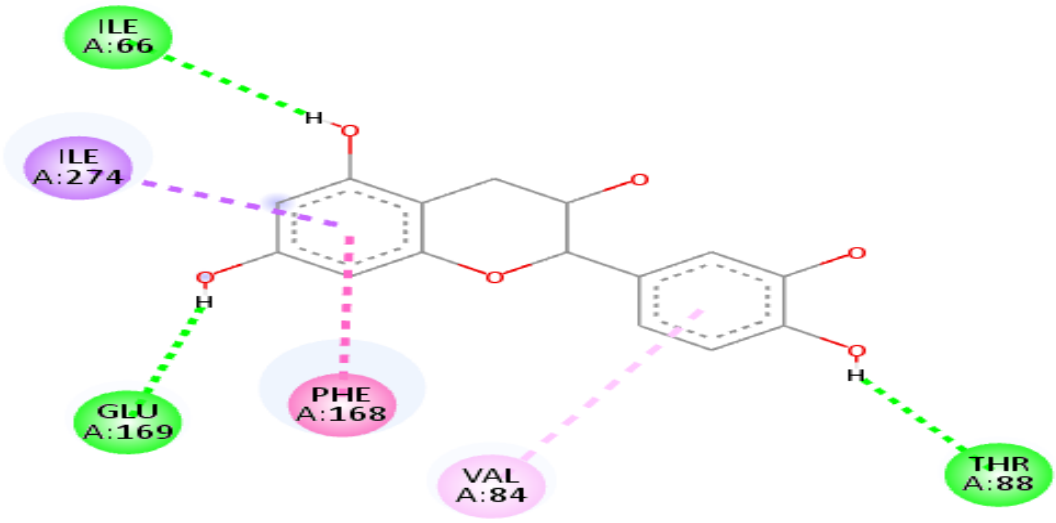


Figure 8: Binding interaction of catechin-3-O-gallate with human adenosine receptor A2A (Generated using Free Version of Discovery Studio Visualizer)

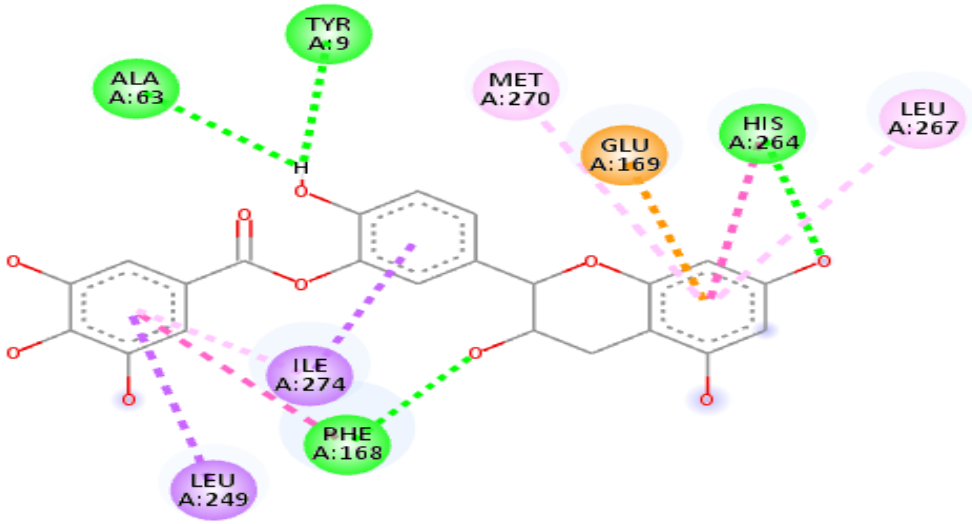


Figure 9: Binding interaction of gallocatechin-3-O-gallate with human adenosine receptor A2A (Generated using Free Version of Discovery Studio Visualizer)

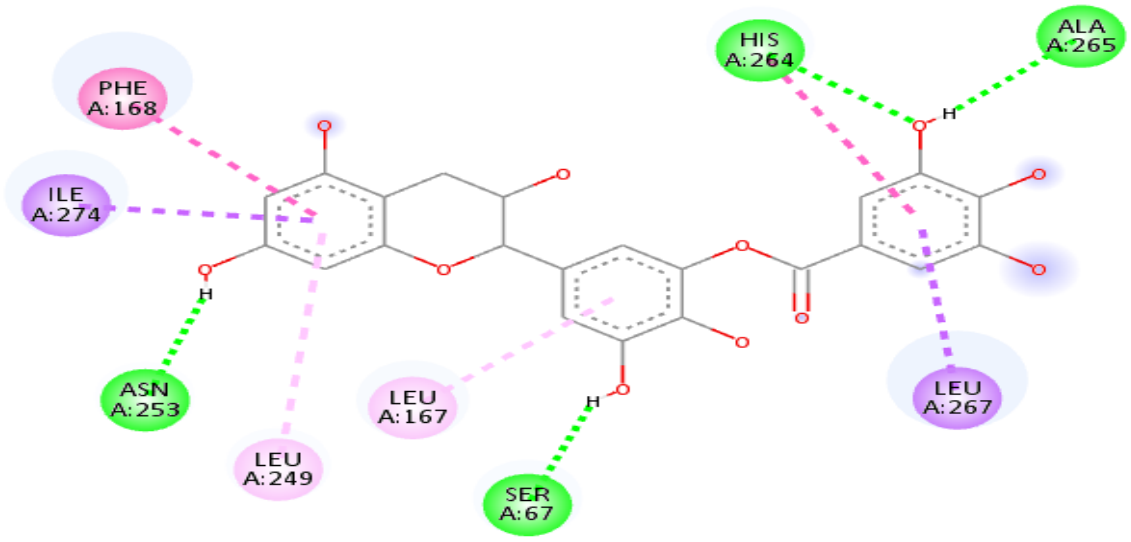


Figure 10: Binding interaction of epigallocatechin-3-O-(3-O-methyl) gallate with human adenosine receptor A2A (Generated using Free Version of Discovery Studio Visualizer

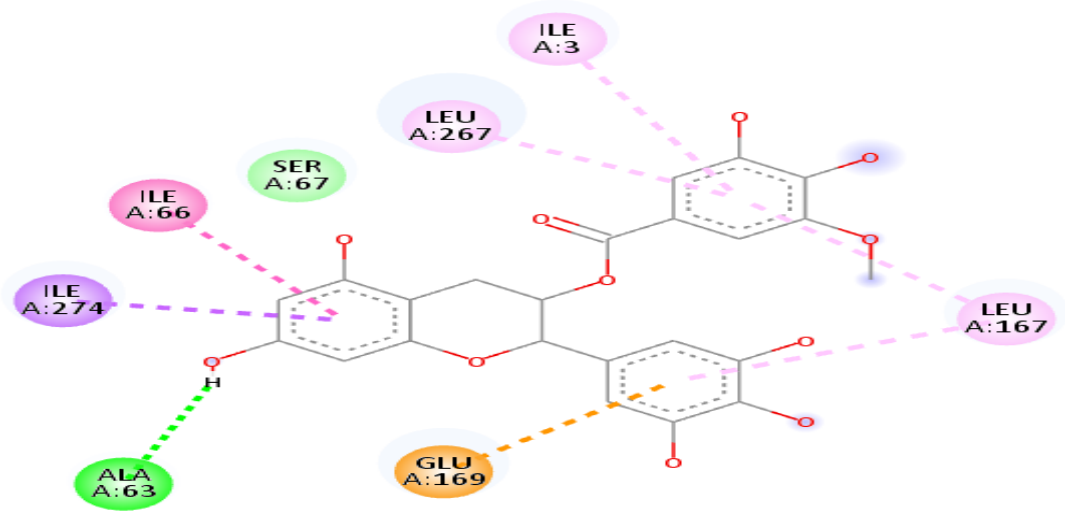


Figure 11: Binding interaction of epicatechin-3-O-(3-O-methyl) gallate with human adenosine receptor A2A(Generated using Free Version of Discovery Studio Visualizer)

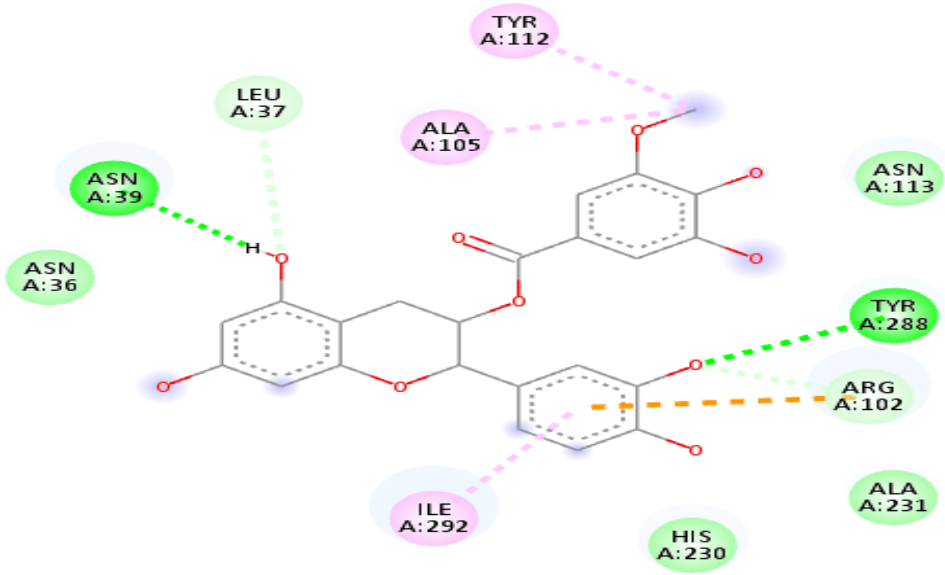


Figure 12: Binding interaction of epigallocatechin gallate with Nav1.7 (Generated using Free Version of Discovery Studio Visualizer)

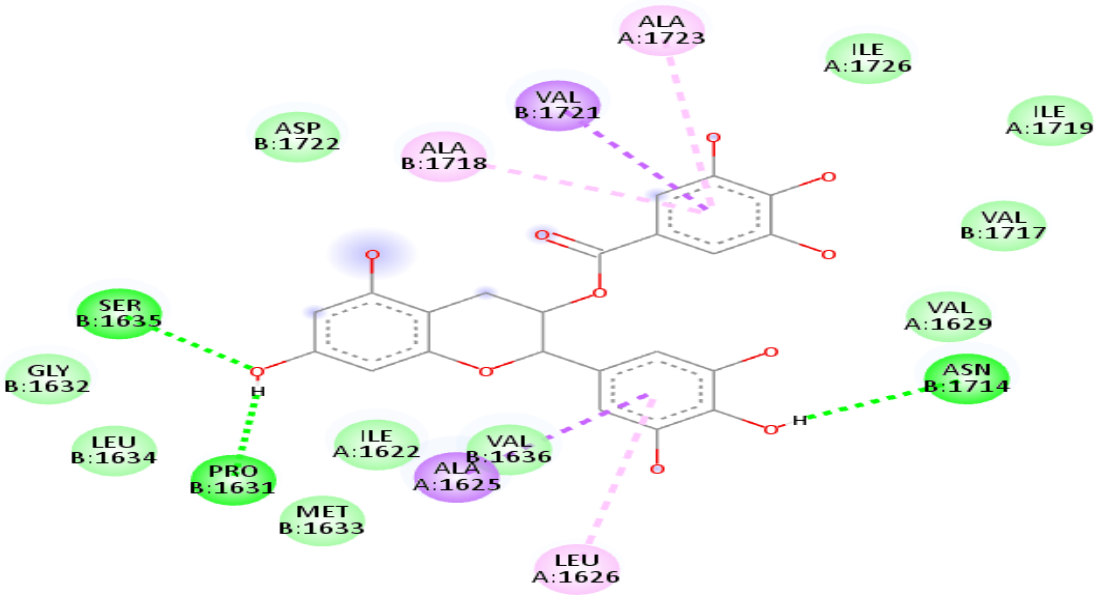


Figure 13: Binding interaction of catechin with Nav 1.7(Generated using Free Version of Discovery Studio Visualizer)

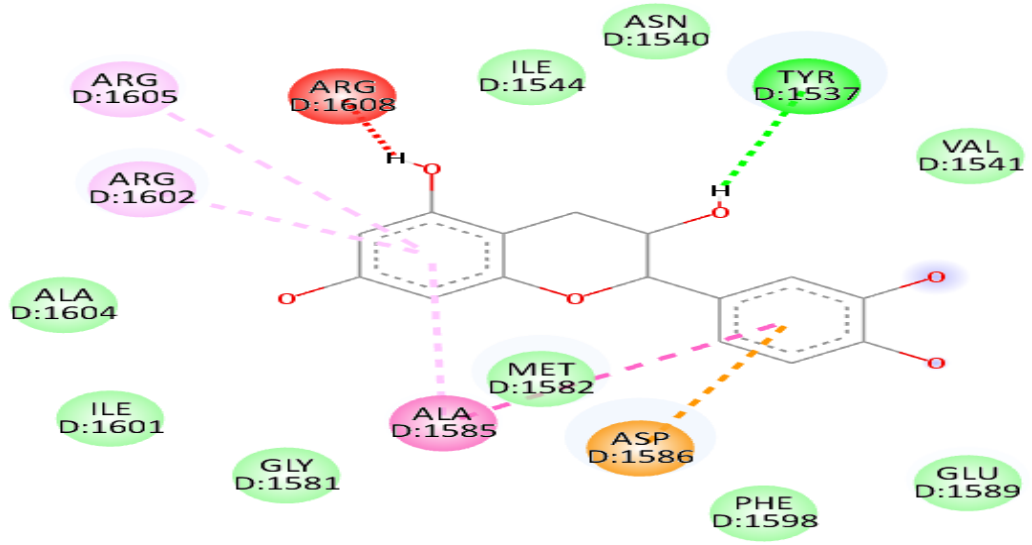


Figure 14: Binding interaction of catechin-3-O-gallate with Nav 1.7(Generated using Free Version of Discovery Studio Visualizer)

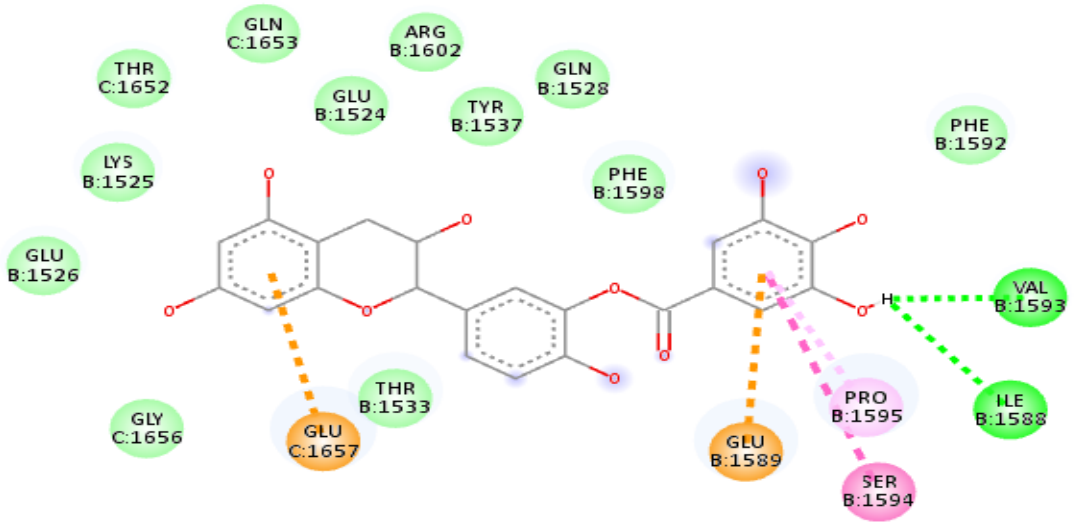


Figure 15: Binding interaction of gallocatechin-3-O-gallate with Nav 1.7 (Generated using Free Version of Discovery Studio Visualizer)

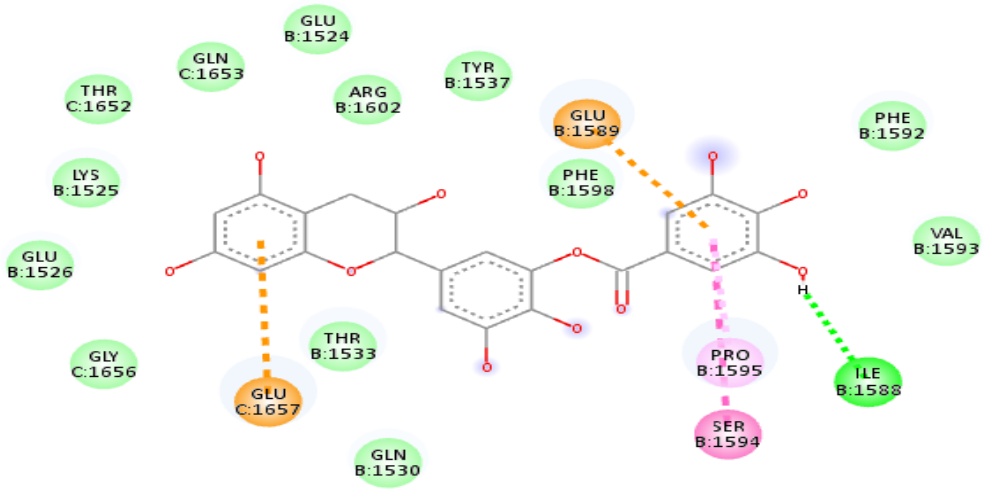


Figure 16: Binding interaction of with epigallocatechin-3-O-(3-O-methyl) gallate Nav 1.7 (Generated using Free Version of Discovery Studio Visualizer)

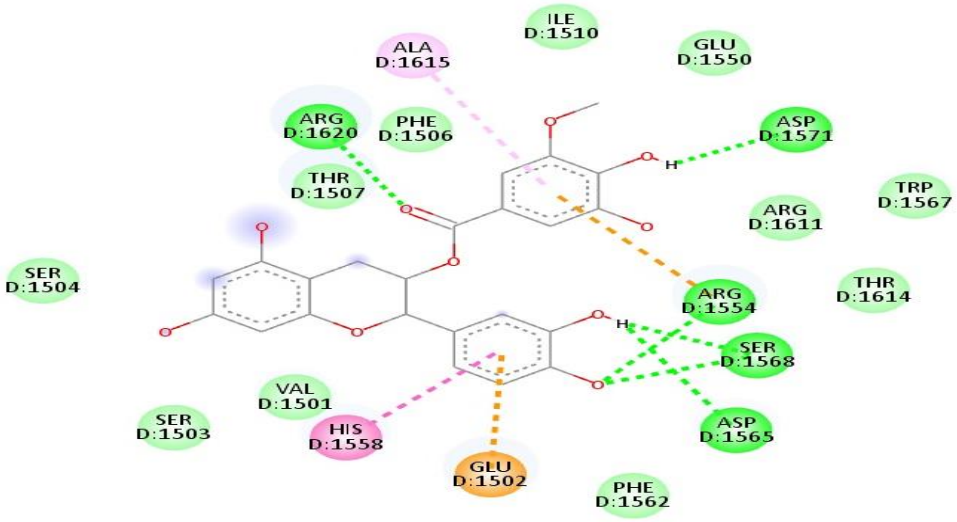
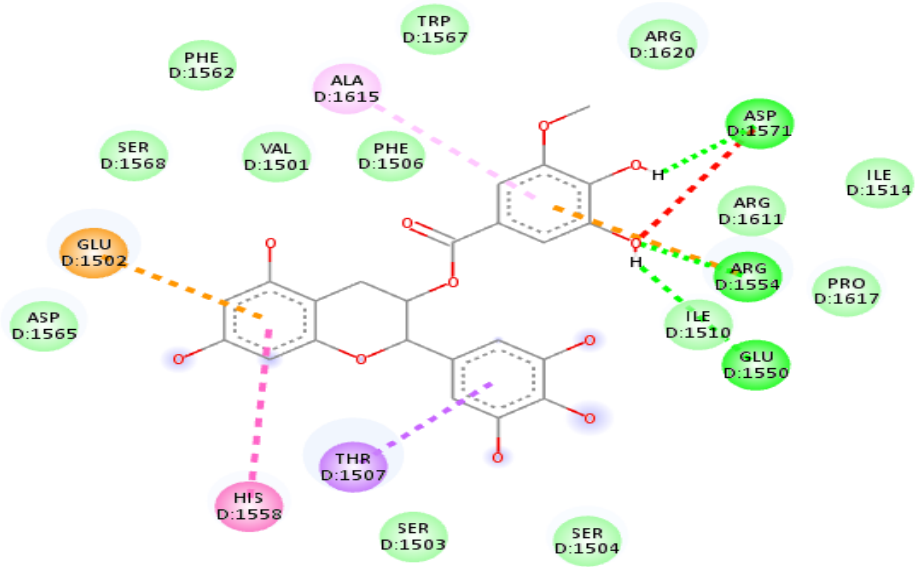


Figure 17: Binding interaction of epicatechin-3-O-(3-O-methyl) gallate with Nav 1.7 (Generated using Free Version of Discovery Studio Visualizer)



Insilico ADME Prognosis

Green Tea Catechins with favourable docking findings were analysed in silico for physicochemical properties using Swiss ADME (www.swissadme.ch) to determine the pharmacokinetic profile of chosen Catechins. As demonstrated in Table No.2, the recognised six Green Tea Catechins have favourable drug-like qualities and a high GI absorption of Catechin, while the others have a low GI absorption.

Table No 2: Insilico ADME parameters of selected Green Tea Catechins

Molecule	Rotatable Bond	#-H bond Acceptor	#-H bond donors	TPSA	iLOGP	GI absorption	BBB permeation
Epigallocatechin gallate	4	11	8	197.37	1.53	Low	No
Catechin	1	6	5	110.38	1.03	High	No
Catechin-3-O-gallate	4	10	7	117.14	1.44	Low	No
Gallocatechin-3-O gallate	4	11	8	197.37	1.37	Low	No
epigallocatechin-3-O-(3-O-methyl)	5	11	7	186.37	2.27	Low	No
gallateepicatechin-3-O-(3-O methyl) gallate	5	10	6	166.14	1.53	Low	No

Pharmacophore Prognosis

The goal was to discover qualities of chosen Green Tea Catechins that inhibit Human Adenosine A2A and Nav 1.7. Pharmacophore Prognosis is a category of attributes that are dominant for interactions with the biological target. For the pharmacophore prognosis of human adenosine receptor A2A and Nav 1.7-VSD4-NavAb, the structures of NECA and GX-936 were employed as references, respectively. For interaction with Adenosine A2A and Nav 1.7, the pharmacophore model revealed the relevance of Hydrogen bond acceptor and donor, Aromatic centre, and Aliphatic groups properties. The developed Pharmacophore Prognosis characteristics of Catechin and EGCG are depicted in fig 18 and fig 19 respectively.

Figure 18: Developed Pharmacophore Prognosis of EGCG

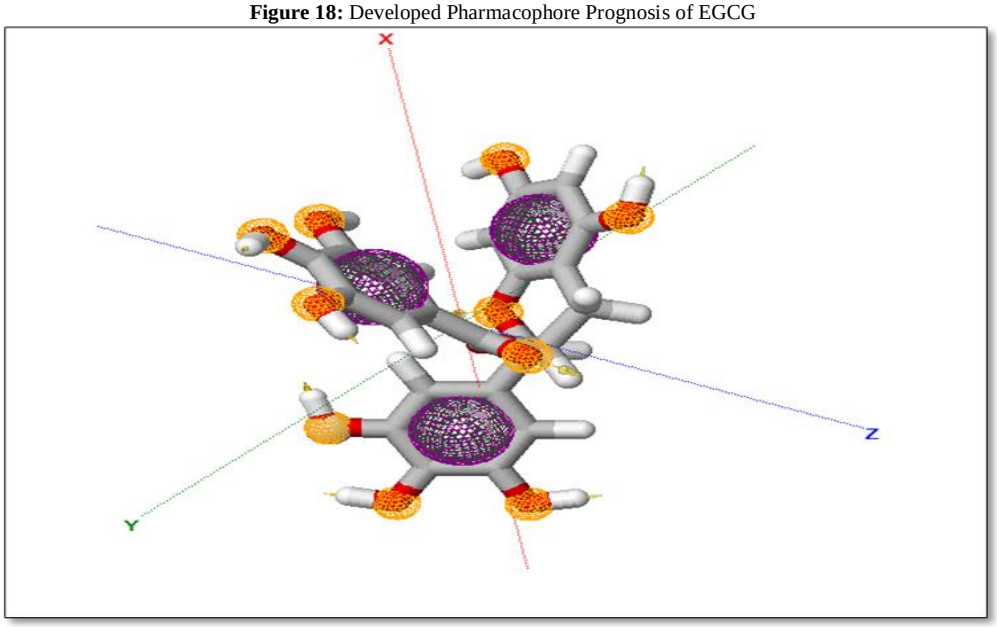
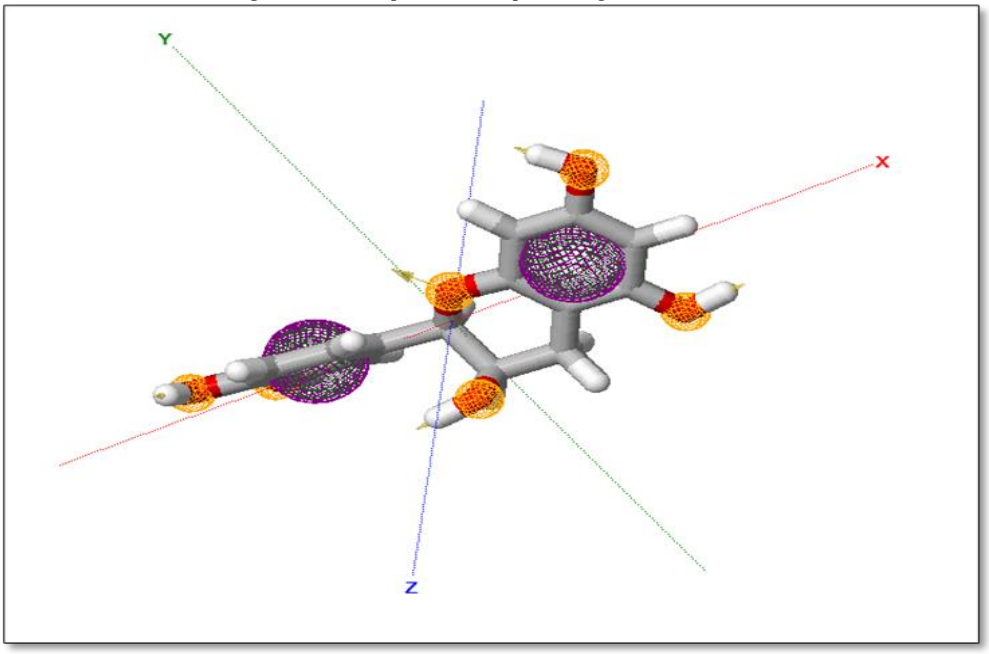


Figure 19: Developed Pharmacophore Prognosis of Catechin



CONCLUSION

Even now, the potency of medications used to treat neuropathic pain is being questioned. We used docking studies of reported Catechins on Adenosine A2A and Nav 1.7 to determine the structural orientation of these compounds. Adenosine A2A Antagonists and Nav 1.7 Inhibitors will continue to be effective supplementary treatments for Neuropathic Pain. Green Tea Catechins showed promise in the treatment of neuropathic pain, with the study revealing that it has a high binding affinity. According to the docking survey Catechin, Catechin-3-O-gallate, Gallocatechin-3-O-gallate, Epigallocatechin-3-O-(3-O-methyl) gallate, Epicatechin-3-O-(3-O-methyl) gallate, Epigallocatechin-3-O-(3-O-methyl) gallate, Epigallocatechin-3-O-(3-O-methyl) gallate, Epigallocatechin-3-O-(3-O- Catechin molecules will connect with Adenosine A2A and Nav 1.7. The catechin docking research revealed that compounds created on these scaffolds will be able to bind with Adenosine A2A and NAV 1.7 and will be free of adverse effects Pharmacophore model revealed the relevance of Hydrogen bond acceptor and donor, Aromatic centre, and Aliphatic groups properties.

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