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Original Article

DECIPHERING THE MOLECULAR BASIS OF NOOTROPIC EFFICACY OF FLAVONOID FROM SEDUM LINEARE THUNB: COMPUTATIONAL APPROACH

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Abstract

Background: Supplements or well-known chemicals that improve cognitive function are called nootropics or smart medicines. They function by enhancing mental faculties like motivation, creativity, memory, and focus. The goal of recent studies has been to identify a novel nootropic that can be made from both natural and synthetic materials. Numerous studies have been conducted on the effects of nootropics on the brain. *Sedum linear Thunb* ,plant is known as "*Sedi linearis Herba*" when used medicinally. Many disorders, such as hepatitis, dysentery, dermatitis rhus, burns, scalds, traumatic bleeding, and a plethora of other conditions, were treated with it on a regular basis.One flavonoid that has demonstrated pharmacological effects and has promise for therapeutic use is quercetin. It is extensively dispersed throughout plants and frequently encountered in diets, mostly in fruits and vegetables. Numerous in vitro investigations have documented quercetin's neuroprotective effects. It has been demonstrated to lower lipid peroxidation and shield neurons from oxidative injury. Apart from its antioxidant characteristics, it also prevents amyloid-β protein fibrils from forming, hence reversing inflammatory cascade pathways and cell lyses.

Aim and Objective: The current study's objective was to assess the Nootropic efficacy of quercetin through *in-silico* molecular docking.

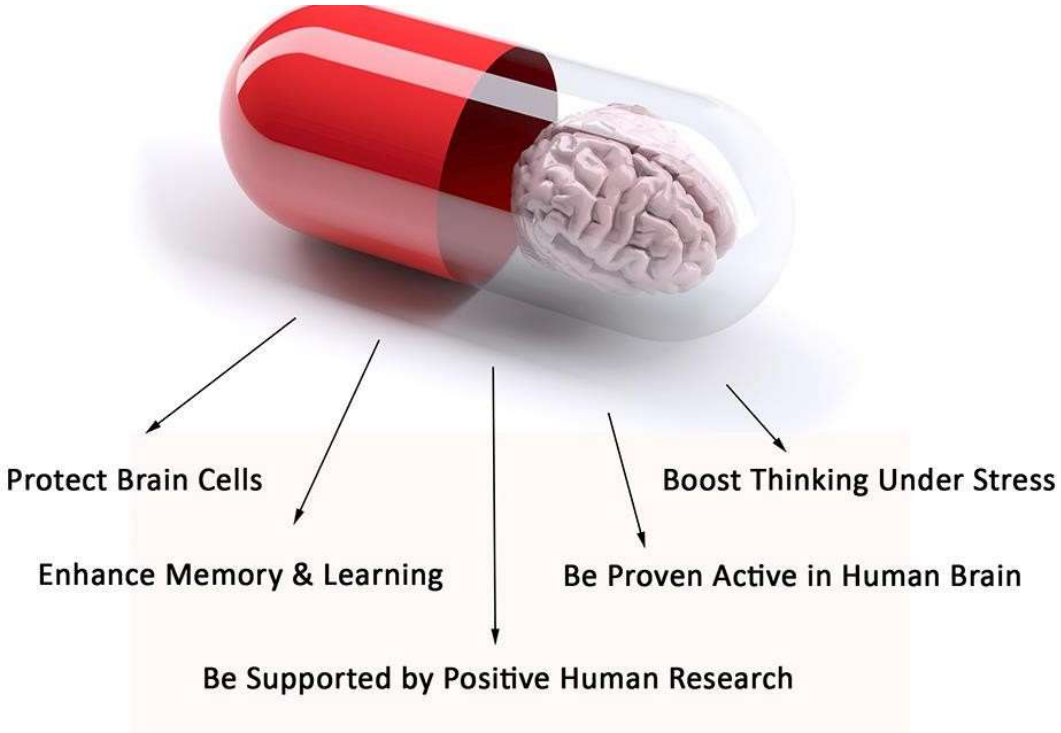
Method: Studies using in-silico molecular modelling were conducted to evaluate the nootropic potential of quercetin by designing it to target both the ***Gluk1 and GluR2*** receptors. The Auto Dock software was utilized to determine the binding through a grid-based docking technique.

Result: The results of the lead molecule's molecular modelling with ***Gluk1 and GluR2*** receptors demonstrated that the chosen compounds had a high affinity for the chosen target protein. It was discovered that the binding energies of quercetin to the *Gluk1 and GluR2* receptors were -5.86 and -7.02 Kcalmol^{-1}, respectively.

Key words: Nootropic efficacy, Quercetin, *Gluk1 and GluR2*receptors.

Introduction

The “nootropic” or simplified as a “smart drug,” “brain booster,” or “memory enhancing drug,” is a common term that will tag along with the compound responsible for the enhancement of mental performance. By definition, nootropic is a compound that increases mental functions including memory, motivation, concentration, and attention.Natural nootropics are proven in boosting the brain function while at the same time making the brain healthier. Nootropics act as a vasodilator against the small arteries and veins in the brain. Introduction of natural nootropics in the system will increase the blood circulation to the brain and at the same time provide the important nutrient and increase energy and oxygen flow to the brain. Despite the 3% weight of total body weight, the brain receives around 15% of the body's total blood supply and oxygen. In fact, the brain can only generate energy from burning the glucose, proving that neuron depends on the continuous supply of oxygen and nutrients [1].



Nootropic Potential

Phytochemicals are best known to reduce the risk of chronic diseases, such as cardiovascular diseases, hypertension, diabetes, and cancers. China refers to the whole *Sedum lineare* Thunb plant used in traditional Chinese medicine as *Sedi linearis Herba*. It was frequently used to treat a variety of illnesses, including hepatitis,

dysentery, dermatitis rhus, burns, scalds, traumatic bleeding, and so forth [2].

Sedum lineare Thunb

Flavonoids are the most diverse group of phytochemicals and are widely distributed in higher plants with outstanding therapeutic potential. Flavonoids are further divided into six classes on the basis of their chemical skeleton: flavanols, flavanones, flavones, flavonols, isoflavonoids, and anthocyanidins. While targeting multiple targets, they have been proven beneficial in the prevention of neurodegenerative disorders and may delay the process of neurodegeneration. Flavonoids are extensively studied for their antioxidant and anti-inflammatory activities, both of which are important in triggering the pathogenesis of AD. Studies suggested that flavonoids are capable of crossing the blood–brain barrier (BBB), which makes them potential agents in preventing neurodegenerative disorders; however, different flavonoid subclasses differ in their ability to cross the BBB [3].As per literature survey it had been found that plant hydro-alcoholic extract is rich source of quercetin and kaempferol. So Quercetin was chosen as lead molecule for *in-silico* docking study

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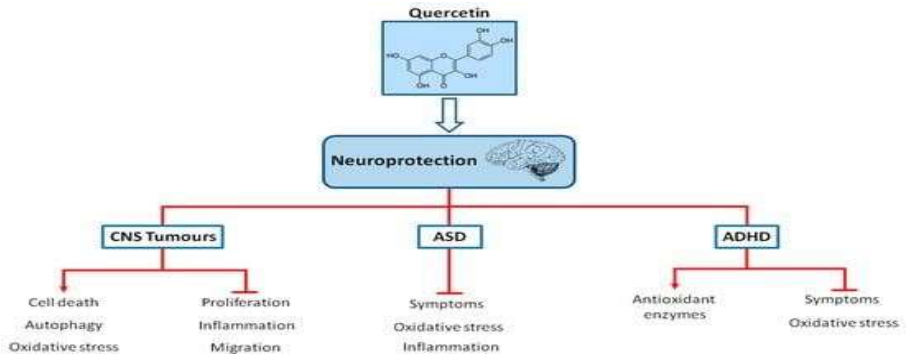
Description of Lead Molecules

Quercetin [4-6]

S.No.	Description	
1.	Molecular formula	$C_{15}H_{10}O_7$
2.	Molecular weight	302.23 g/mol
3.	Source	Apples, berries, Brassica vegetables, capers, grapes, onions, shallots, tea, and tomatoes.
4.	Category	Flavonol
5.	Pharmacology	Immune system stimulation and anti-inflammation. Numerous biological processes, including glucose homeostasis, insulin secretion and sensitization, peripheral tissue glucose uptake, and intestinal glucose absorption inhibition, are impacted by quercetin.

Neuroprotective Potential of Quercetin



Experimental Work

Molecular docking studies Quercetin against *GluK1 and GluR2* receptor

Ligand Preparation:

2D Structure of quercetin was drawn using ChemSketch [7], the two-dimensional structure of the prepared ligand was converted into their 3-D structures optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligand were given below:

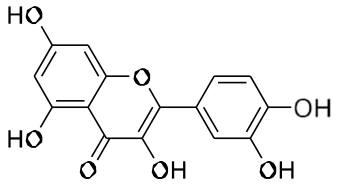


Figure 1: 2D structure of quercetin

Preparation of the grid file

The regions of interest used by Autodock weredefined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing and grid points for all the considered receptors in the current study are given in table 1 [8].

Table 1. Grid parameters used in current docking analysis of GluK1 and GluR2 receptor.

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	y center	z center
1	GluK1	40	40	40	0.375	11.98	4.435	-7.653
2	GluR2	40	40	40	0.408	31.132	2.235	-15.672

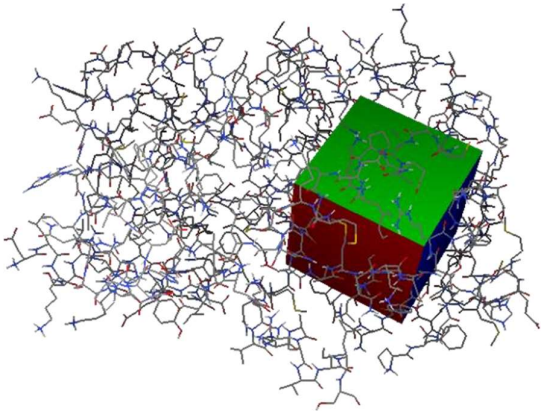


Figure 2: Grid box covering all active sites in GluK1 receptor

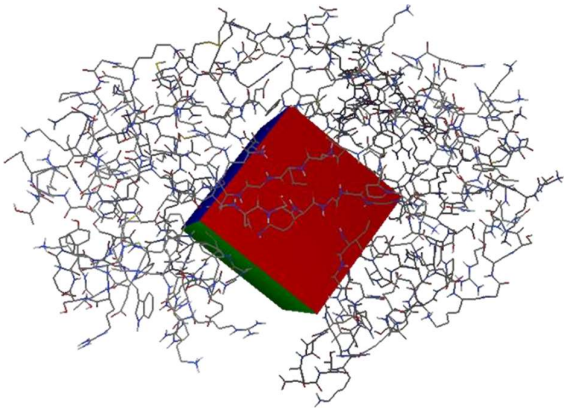


Figure 3: Grid box covering all active sites in GluR2 receptor

Preparation of the docking file

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [9-10].

Docking Study

Crystal structure

The crystal structure of the protein consisting of GluK1 and GluR2 receptor is downloaded from the Protein Data Bank portal. All the primary information regarding all the receptor's structure was registered in the Protein data bank [11-12]. The complex ligand was separated by using Chimera software for all the target receptors.

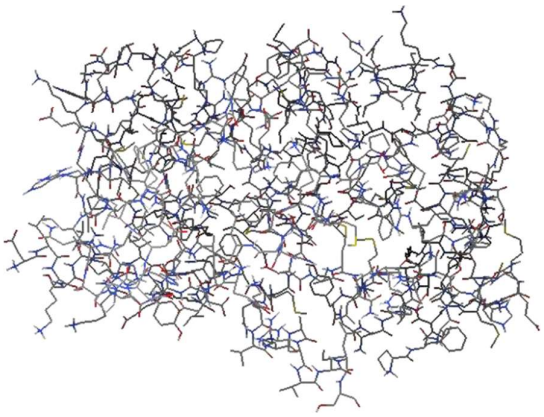


Figure 4: Crystal structure of GluK1 receptor (PDB ID-2zns)

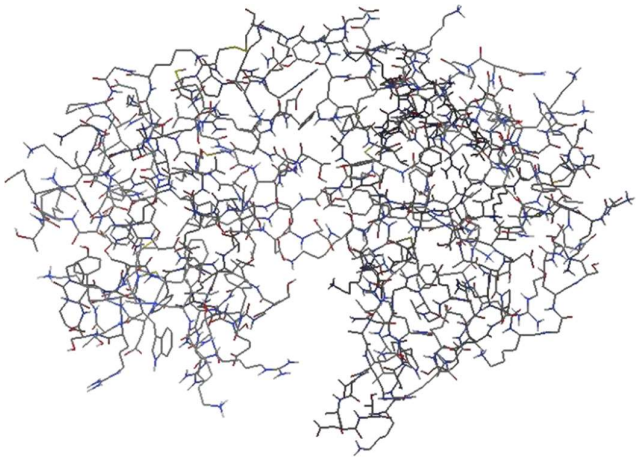


Figure 5: Crystal structure of GluR2 receptor (PDB ID-3r7x)

Processing of Protein

All the downloaded receptor proteinsare having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand wasseparated from the macromolecular complex by using software Chimera [13-14].

Molecular Docking Simulation Studies

Docking of ligand quercetin against GluK1 and GluR2 receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [15-18].

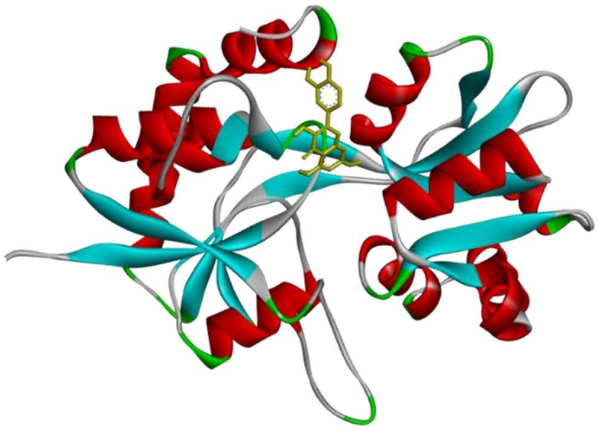


Figure 6: Binding mode of quercetin within the active site of GluK1 receptor

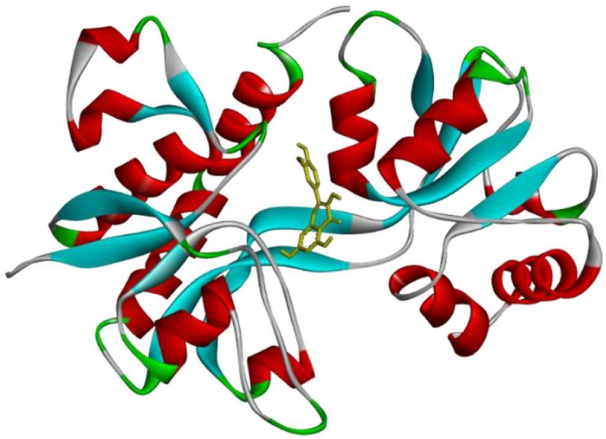


Figure 7: Binding mode of quercetin within the active site of GluR2 receptor

Toxicity & ADME-T Studies

The ligand molecules viz. quercetin was studied by online program OSIRIS, for prediction of presence of any toxicgroup as well as presence of any toxic group and ADME- T properties [19].

Result and Discussion

Green pigments found in many plants are made of flavonoids, a broad class of naturally occurring chemicals that are biosynthesized from phenylalanine. Medical professionals have traditionally used flavonoids to treat a wide range of illnesses. They are a major class of medicinal agents due to their enormous diversity, widespread distribution, and ease of isolation. Flavonoids are essential for the synthesis of many different medications and can also be employed as natural products, making them important components in the field of drug design and discovery. According to recent research, eating foods high in flavonoids on a regular basis can significantly improve cognitive function in people. Furthermore, a number of flavonoids have been shown to slow the development of Alzheimer's disease (AD) pathology. This is due to their capacity to mitigate cognitive deficits in a variety of transgenic and normal preclinical animal models. Foods high in flavonoids, such as chocolate, green tea, and blueberries, have health benefits because flavonoids and their metabolites interact with a variety of cellular and molecular targets.Quercetin was chosen as the lead molecules for investigation of nootropicefficacy. Molecular docking research using computational methods was used to evaluate Nootropic potential of the lead molecule.The glutamatergic system remains an attractive chemical target for pharmaceutical intervention. Ligands acting on ionotropic glutamate receptors (iGluRs: NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isooxazolepropionic acid and kainate receptors) and metabotropic glutamate receptors are potential treatment options for neurodegenerative diseases, epilepsy, schizophrenia, anxiety, and memory disorders (mGluRs). However, very few glutamate receptor ligands turned out to be helpful in therapeutic situations. Particularly promising seem to be ligands of the kainate receptor subfamily. The mossy fibre long-term potentiation pathway, which is crucial for epileptogenesis and causes synaptic plasticity, is mostly mediated by kainate receptors. Thus, kainate receptor antagonists may be used as anti-seizure and neuroprotective drugs. The GluR2 subunit of the AMPA receptor (AMPAR) controls the essential biophysical characteristics of the receptor, exerts significant influence over receptor trafficking and assembly, and is essential for certain types of long-term synaptic plasticity. This crucial subunit is present in the majority of neuronal AMPARs; nevertheless, AMPARs lacking this subunit can be expressed in specific restricted neuronal populations and in specific physiological or pathological circumstances. Such GluR2-lacking Ca^{2+}-permeable AMPARs are currently attracting a lot of

attention due to their potential impact on the regulation of synaptic transmission.

Quercetin's molecular docking with the GluK1 and GluR2 receptors demonstrated that it has demonstrated a chemical interaction with the amino acids in the active pockets, as depicted in Figures 6–7 (Table 3). In theory, quercetin has demonstrated a promising docking score. Quercetin's docking result showed that it had docking scores of -5.86 and -7.02 kcal mol^{-1}, respectively, with GluK1 and GluR2 receptors. This suggests that quercetin is a powerful inhibitor of these receptors. The lead molecule's 3D and 2D binding affinities against particular receptors are depicted in figures 8-9 and 10–11 respectively. The binding interaction of lead molecules against selected receptors was tabulated in table 3, which revealed lead molecule quercetin interaction with GluK1 receptor revealed CH & Pi-sigma bonding whereas CH and Pi-alkyl binding interaction showed by quercetin with Glu R2.

Table 2: Results of docking of ligands like quercetin against GluK1 and GluR2 receptors

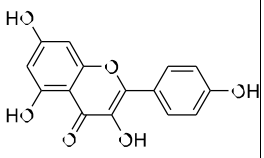
S. No	Compound Name	Structure	GluK1	GluR2
1	Quercetin		-5.86 (ki: 50.94µM)	-7.02 (ki: 7.15µM)

Table 3: Binding interaction of lead molecule with receptor

Lead molecule & Receptor	CH-bonding	Covalent bonding	Vander Waals interaction	Pi-Alkylbonding	Pi-Sigma bonding
Quercetin with GluK1 receptor	Gln427 Asp 707 Val 430 Tyr 432	----------	Leu 425 Glu 426	----------	Met 431 Lys 434

Quercetin with GluR2 receptor	Pro 89 Tyr 220 Glu 13 Ser 14	Tyr 61	Arg 96 Leu 90 Thr 91 Pro 15 Tyr 199 Trp 225 Thr 195 Tyr 16 Thr 174	Met 196	

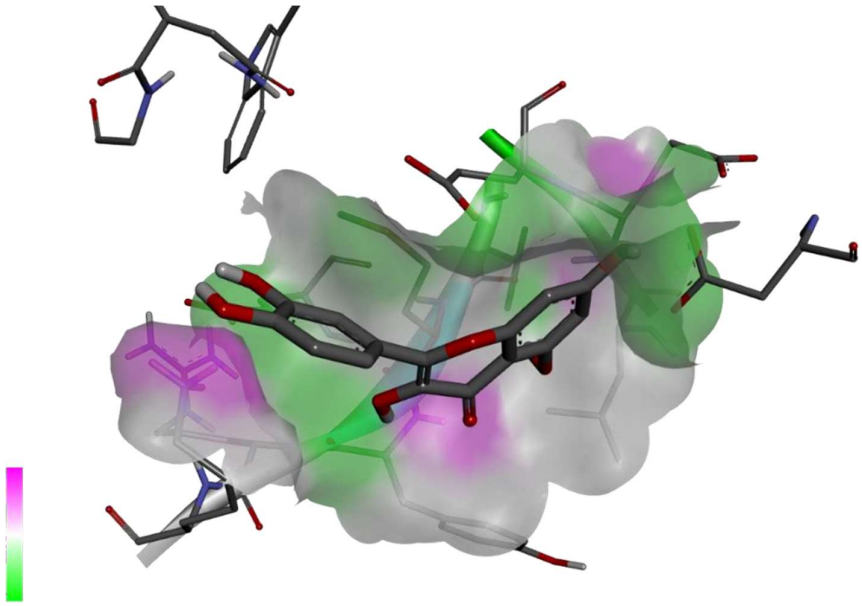


Figure 8: Three-dimensional binding mode of quercetin within the active site of GluK1 receptor

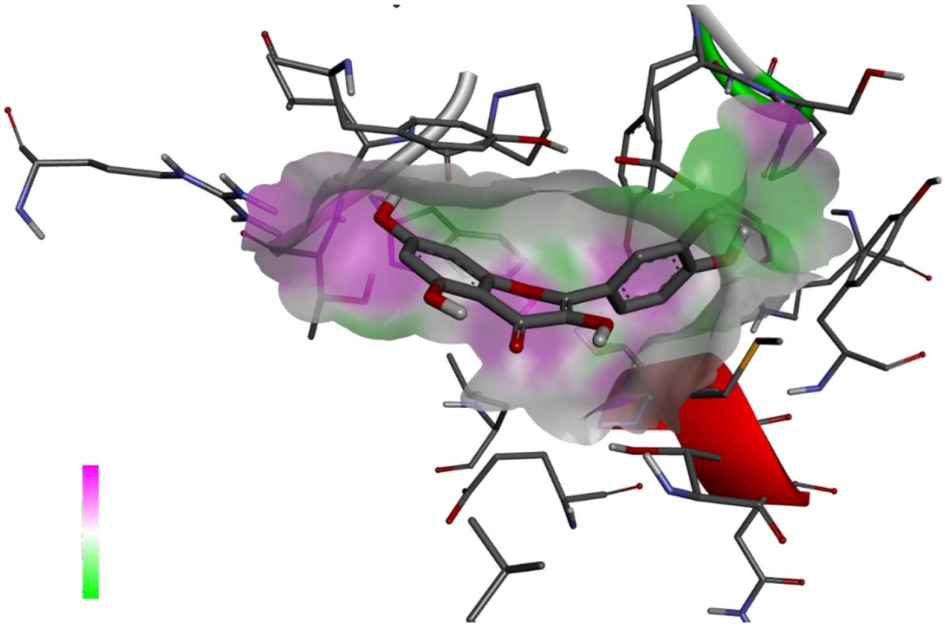


Figure 9: Three-dimensional binding mode of quercetin within the active site of GluR2 receptor

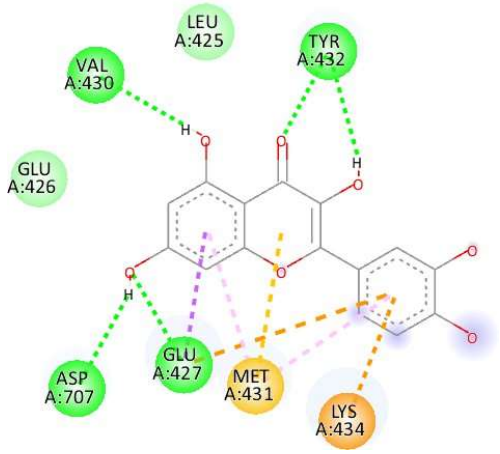


Figure 10: Two-dimensional binding mode of quercetin within the active site of GluK1 receptor

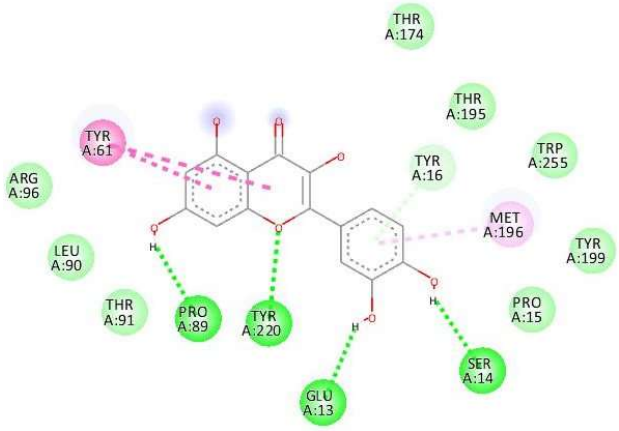


Figure 11: Two-dimensional binding mode of quercetin within the active site of GluR2 receptor

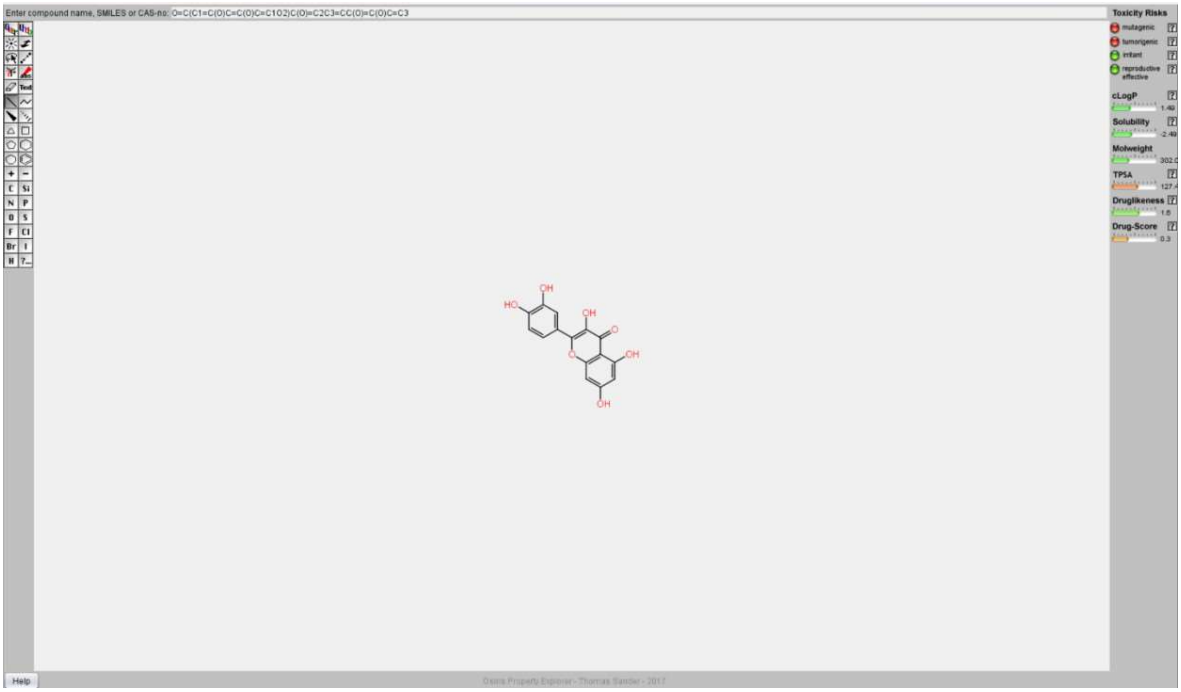
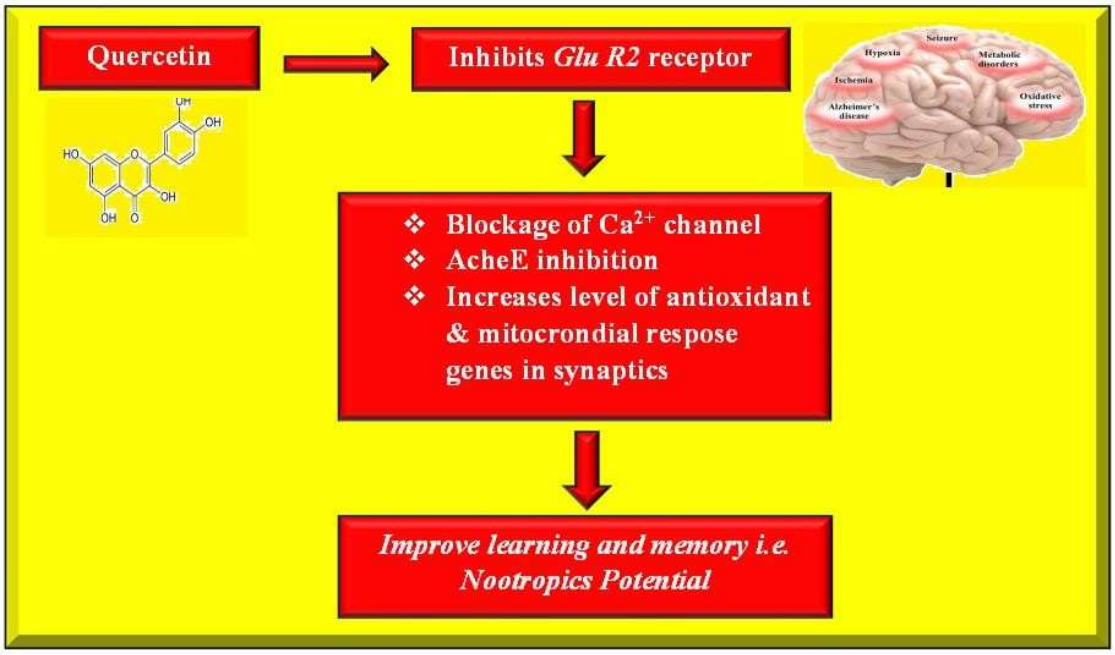


Figure 12: Pharmacokinetic and toxicity profiling of quercetin

Divulugence of Investigation

The ancient medical system known as Ayurveda created therapeutic treatments for a wide range of illnesses. Agents that can postpone ageing and revitalise the body's entire functioning dynamics have been developed. The name of this type of rejuvenation therapy is "Rasayana chikitsa" (rejuvenation therapy). According to Ayurveda, a number of plants known as

"Medhya" plants—herbs that promote intellect—are helpful for treating cognitive issues. In order to treat dementia, medications and natural therapies are now recommended to improve memory and guard against memory impairments in the brain. Herbs used as memory boosters improve cognition and improve cerebral blood flow. With varying degrees of success, nootropics have been used to treat degenerative brain illnesses like Alzheimer's and Parkinson's disease. It has been demonstrated that quercetin possesses neuroprotective and anti-inflammatory qualities. Additionally, it can activate AMP-activated protein kinase (AMPK), a cellular energy sensor that regulates oxidative stress and inflammation. In treating neurodegenerative illnesses and other brain disorders, quercetin shows promise as a safe and efficacious supplementary therapy since it lowers inflammation and guards against neuroinflammatory damage. *S. lineare* Thunb as a potential source of bioactive compounds was demonstrated since past era. The presence of diverse phytoconstituents, significant levels of phenols and flavonoids, and the identification of quercetin offer promising avenues for future research and the development of natural therapeutics.According to the results of the current study, quercetin effectively boosts memory by inhibiting the GluK1 and GluR2 receptors with a high affinity for the GluR2 receptor. The finding of current investigation showed that the lead compound (quercetin) found in *S.linear*ejustify the memory enhancer potential. The fundamental deciphering was represented graphically as follows:



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