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Original Research Article

Molecular Docking Based Predictive Study of Bougainvillea Glabra against *Mtorc1* Protein for the Treatment of Diabetic Nephropathy: Network Pharmacology

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Abstract

Background: The decline in kidney function experienced by people with type 1 and type 2 diabetes who are chronically ill is known as diabetic nephropathy (DN) or diabetic kidney disease. The condition is known to progress in a number of stages and is related to blood pressure and glycemic management. Nevertheless, despite strict blood sugar management, the prevalence of chronic kidney disease (CKD) in diabetic patients has not decreased over the past 20 years, which has led to the discovery of new risk factors for the illness's development. The medical characteristics of the Paper Flower, Bougainvillea spectabilis, include anti-inflammatory, anti-hepatotoxic, anti-inflammtory, anti-hyperlipidemic, antibacterial, antioxidant, and antiulcer capabilities. Alkaloids, flavonoids, glycosides, phenolics, phytobannins, quinones, saponins, tannins, and terpenoids are examples of phytoconstituents that have been claimed to have medicinal characteristics. ***Method:*** In the current study, a molecular docking technique was used to try and identify ***mTORC1***protein inhibitors. A grid-based docking strategy was used to determine the binding using the Auto Dock software. Merck Molecular Force Field was used to build the 2D structures of compounds, convert them to 3D, and then energetically reduce them up to arms gradient of 0.01. (MMFF). ***Result:*** The molecular docking of Ferulic acid & Gallic acid with ***mTORC1*** protein showed binding energy (Kcal/mol) -5.37 & -4.56 respectively. ***Conclusion:*** Theoretically, all the ligand molecules have shown encouraging docking score. The docking result of ferulic acid revealed that their docking scores was -5.37 kcal mol^{-1}, and it can be predicted as good inhibitor of ***mTORC1*** protein and thereby prevents dysregulation of intracellular protein synthesis and the metabolic balance along with decreasing oxidative stress on the kidney.

Keywords: Diabetic nephropathy, Ferulic acid, Gallic acid, *mTORC1* & molecular docking.

INTRODUCTION

A similar epidemic of these conditions' consequences has resulted from the worldwide prediabetes and diabetes epidemics. The most frequent complication is neuropathy, of which distal symmetric polyneuropathy (also known as diabetic neuropathy for the purposes of this Primer) is particularly common. Diabetic neuropathy is marked by discomfort and significant morbidity, as well as a loss of sensory function that begins distantly in the lower limbs. At least 50% of people with diabetes eventually develop diabetic neuropathy. In patients with type 1 diabetes mellitus, glucose management significantly slows the evolution of diabetic neuropathy; however, the effects are less pronounced in patients with type 2 diabetes mellitus. These discoveries have sparked renewed research into the causes of diabetic neuropathy and new suggestions for how to prevent and cure this condition in 2017 that are tailored to each type of diabetes [1]. With the progression of the condition, diabetic neuropathy prevalence also shifts. In fact, when individuals with T2DM were followed up on for 10 years, the prevalence of diabetic neuropathy rose from 8% to 42%19. In the Danish Addition trial, participants with newly identified screen-detected T2DM23 had a prevalence of diabetic neuropathy of 13% at study entrance, with a cumulative incidence of 10% over the 13-year follow-up period in a group of patients with very mild T2DM who maintained good metabolic control. The incidence of diabetic neuropathy over the course of four years was 66–72 percent in patients who did not have neuropathy at baseline17 in a large cohort of patients with more advanced T2DM and verified coronary artery disease who were taking part in the BARI 2D experiment.

Effective diagnostic, screening, and preventative techniques are crucial given how frequent neuropathy is in people with diabetes [2].

Pathophysiology

Diabetes-related neuropathy is a rare form of peripheral nervous system neurodegeneration that primarily affects sensory, autonomic, and eventually, to a lesser extent, motor axons. There is disagreement over how diabetes mellitus affects sensory neurons. Terminal sensory axons in the periphery shrink and "die back" as a result of progressive diabetic neuropathy, while the perikarya is relatively unaffected (cell bodies). For this reason, diabetic neuropathy is regarded as a length-dependent neuropathy. Its "stocking and glove" pattern of involvement reflects damage to the longest sensory axons first, with, for example, loss of distal leg epidermal axons preceding loss in more proximal limbs. There is strong experimental support for the idea that diabetes affects the entire neuron, from the perikaryon to the terminal. However, there is disagreement about whether damage first affects peripheral axons and the Schwann cells that are connected with them or the neuron perikarya that are found in the dorsal root ganglia (DRG) and function to maintain the axons [3].

The importance of medicinal plants to the wellbeing of people and communities cannot be overstated. As the "Emporium of Medicinal Plants," India is well known. The demand for medicinal plants has multiplied due to their significant importance [4]. The Bougainvillea genus is one of the most widely distributed plant families in the world. According to "The Plant List," it is a member of the Nyctaginaceae family and has about 18 species [5]. With an emphasis on their morphological aspects, phytochemistry, and pharmacological efficacy, this review's goals aim to provide a recent update on Bougainvillea glabra. Louis de Bougainville, a cosmopolitan adventurer, discovered the Brazilian plant in the 18th century, introduced it to Europe, and gave it the name "bougainvillaea" after him [6]. Because its bracts are thin and papery, the bougainvillaea is also known as the "paper flower."

Bougainvillea glabra

Phytochemistry of B.glabra

Initial phytochemical analysis of leaves in various extracts found alkaloid, glycosides (in small amounts), flavanoids, tannins, steroid, protein, and saponins. B. glabra's leaves and flowers are a particularly abundant source of phenolic chemicals [7].

Phyopharmacology of *B.glabra*

Bouainvillea glabra has antimicrobial, antiulcer, antidiarrheal, and cough and sore throat therapeutic properties. The plant is also used to treat leucorrhea and heptatitis, acting as an antacid to lessen acidity. However, B. glabra also has antibacterial, anti-diabetic and antifertility properties. Additionally, Bougainvilea has anti-inflammatory and antioxidant properties [8-12].

EXPERIMENTAL WORK

Molecular docking studies

Ligand Preparation:

2D Structure of ligands like gallic acid & ferulic acid were drawn using ChemSketch[13], the two-dimensional structures of the prepared ligands were converted into their 3-D structures optimized with 3D geometry. The optimized structures were saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligands were given below:

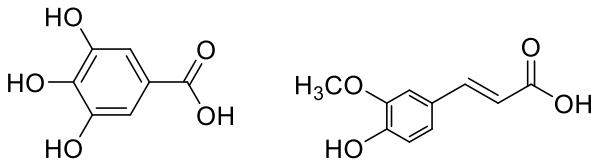


Figure 1: 2D structure of gallic acid & ferulic acid

Preparation of the grid file

The regions of interest used by Autodock were defined 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 between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.375 Å and No. of points considered are 40, 40 and 40 points in the x, y, and z dimensions and -17.444, -6.567 and -49.421 as x, y, z centers [14].

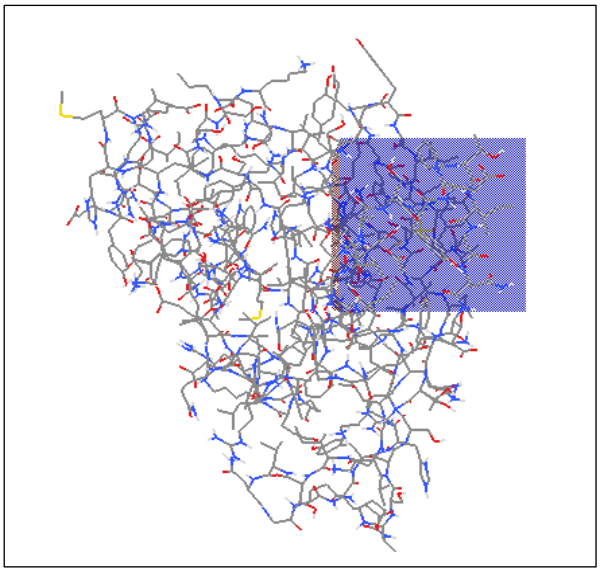


Figure 2: Grid box covering all active sites in mTORC1 receptor

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [15].

Crystal structure

The crystal structure of the protein consisting of mTORC1 receptor is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (6bsx.pdb) registered in the Protein data bank was used [16]. The complex ligand was separated by using Chimera software.

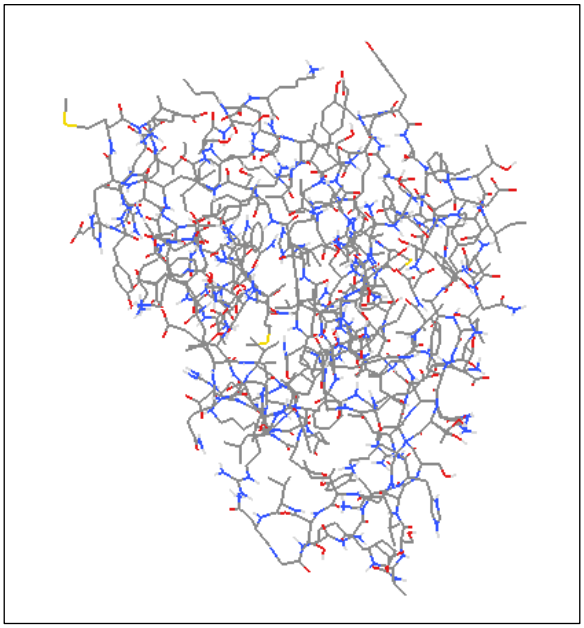


Figure 3: Crystal structure of mTORC1 receptor (PDB ID-6bsx)

Processing of Protein

The downloaded receptor protein is having five chains, i.e. chain A, B, C, D, and E. Out of these five chains, chain A was selected for experimental purpose and other chains were removed from it. The bound ions were separated from the macromolecular complex by using software Chimera [17].

Molecular Docking Simulation Studies

Docking of ligands like gallic acid & ferulic acid against human mTORC1 receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [18].

Toxicity & ADME-T Studies

The ligand molecules viz. gallic acid & ferulic acid were studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [19, 22].

RESULT AND DISCUSSION

Phenolic compounds, widespread in plants, are a necessary part of the human regimen due to their antioxidant and pro-oxidative properties. Naturally, phenolics structurally range from a very simple phenolic molecule moiety to an intricate polymer. For decades, phenolic compounds have gained pronounced attention because of their protective effects against degenerative disorders such as inflammation, diabetes and cancer.

Many natural products have been studied *in-silico*, *in-vitro* and *in-vivo* assays to restrain hyperglycemia. In addition, natural products, and particularly polyphenols, possess diverse structures for exploring them as inhibitors of α-glucosidase and α-amylase. Interestingly, an *in- silico* discovery approach using natural compounds via virtual screening could directly target α-glucosidase and α-amylase enzymes through *Monte Carto* molecular modelling.

Hyperglycemia causes a rise in intracellular glucose levels, which reduces AMP kinase activity and promotes ***mTORC1***. Hyperinsulinemia and extra amino acids brought on by overeating are additional conditions necessary for enhanced ***mTORC1*** activity, which is seen not just in the kidneys but also in other organs including adipose tissue and the liver. This is in addition to hyperglycemia, obesity, and type 2 diabetes. Increased endoplasmic reticulum stress and intracellular oxidative stress can result from excessive ***mTORC1*** activation, which can also affect the metabolic balance and intracellular protein production. In glomerular disorders, such as DKD, the proximal tubules reabsorb a significant amount of urine proteins from the glomerulus, overloading the tubular cells and causing inflammation and fibrosis of the tubular interstitium, which ultimately results in a reduction in renal function. Interestingly, albumin reabsorption causes autophagy to occur in

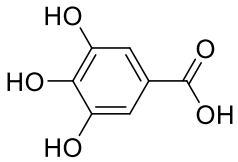
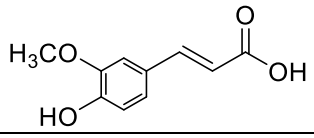
proximal tubular cells [21]. Furthermore, obese type 2 diabetic mice given a high-fat diet have active ***mTORC1***, which inhibits the autophagy brought on by urine proteins. The activation of ***mTORC1*** inhibits the cytoprotective autophagy brought on by urine proteins in diabetic proximal tubular cells. As a result, cytotoxicity brought on by urine proteins is produced. In obese type 2 diabetes, rapamycin, a ***mTORC1*** inhibitor, reduces excessive ***mTORC1*** activity and prevents tubular cell damage.

Bougainvillea glabra (Choisy). (Family: Nyctinaginacea) is a valuable ornamental plant with culinary uses and also utilized in traditional medicine for treating common ailments. It is traditionally employed against several diseases such as diarrhoea, hypotension, intestinal disorders, stomachic, nausea, inflammation-related ailments, and in pain management. The extract of its leaves contains pinitol, which serves as hypoglycemic agent and exhibits insulin like effect (Pratibha Chauhan *etal* 2016). Glucosidase inhibitory activity of *B spectabilis* against murine pancreatic and intestinal glucosidase is suggested to be one of the important underlying mechanisms of antidiabetogenic activity [20].

As per literature survey and ethano-pharmacological uses of *Bougainvillea glabra*, the present study was undertaken to investigate the protective and therapeutic potential Bougainvillea glabra against Diabetic nephropathy via. Molecular docking. Computational based analysis based on interaction of phenolic compound found in the plant with ***mTORC1*** protein.

The molecular docking of Ferulic acid & gallic acid with ***mTORC1*** protein showed binding energy (Kcal/mol) -5.37 & -4.56 respectively. The result was tabulated in table 1 and binding mode of phenolic compounds found in *Bougainvillea glabra* displayed in fig.4-5. The molecular interaction of selected compound shown in fig.8-9(2D) &10-13 (3D). As per outcome of the investigation binding energy of Ferulic acid shown good interaction with ***mTORC1*** protein having conventional hydrogen bonding at Gln A:64, PHE A:74, ILE A:69SER A: 68, TYR A:81,SER A:75 & TYR A:74 along with Pi- sigma bonding with ILE A:78, ALA A:10 & VAL A:59 with MET A:106(covalently).The outcome of investigation showed that both selected phenolic compounds found in *Bougainvillea glabra* are more or less potent ***mTORC1*** protein inhibitor and effectively with selected ligand but ferulic acid exhibited potent inhibitor of ***mTORC1*** protein. The pharmacokinetic profile of ferulic acid reveals that it is having good pharmacokinetic profile but with the presence of any major toxic effects including mutagenicity, tumorigenicity and reproductive effects. The pharmacokinetic and toxicity profiling results of ligands like gallic acid & ferulic acid were shown in figure 6-7.

Table 1: Results of docking of ligands against human *mTORC1* receptor

Sl. No	Compound Name	Structure	Binding Energy (Kcal/mole)
1	Gallic acid		-4.56
2	Ferulic acid		-5.37

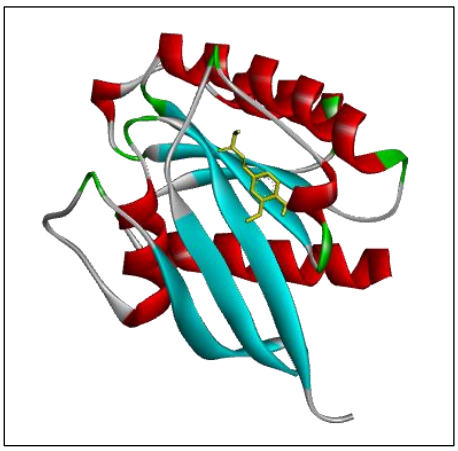


Figure 4: Binding mode of gallic acid within the active site of human mTORC1 receptor

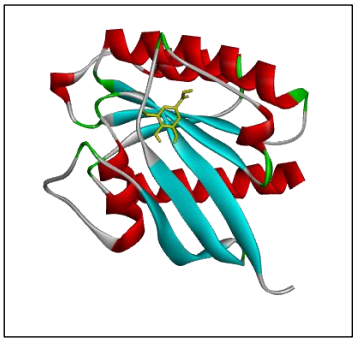


Figure 5: Binding mode of ferulic acid within the active site of human mTORC1 receptor

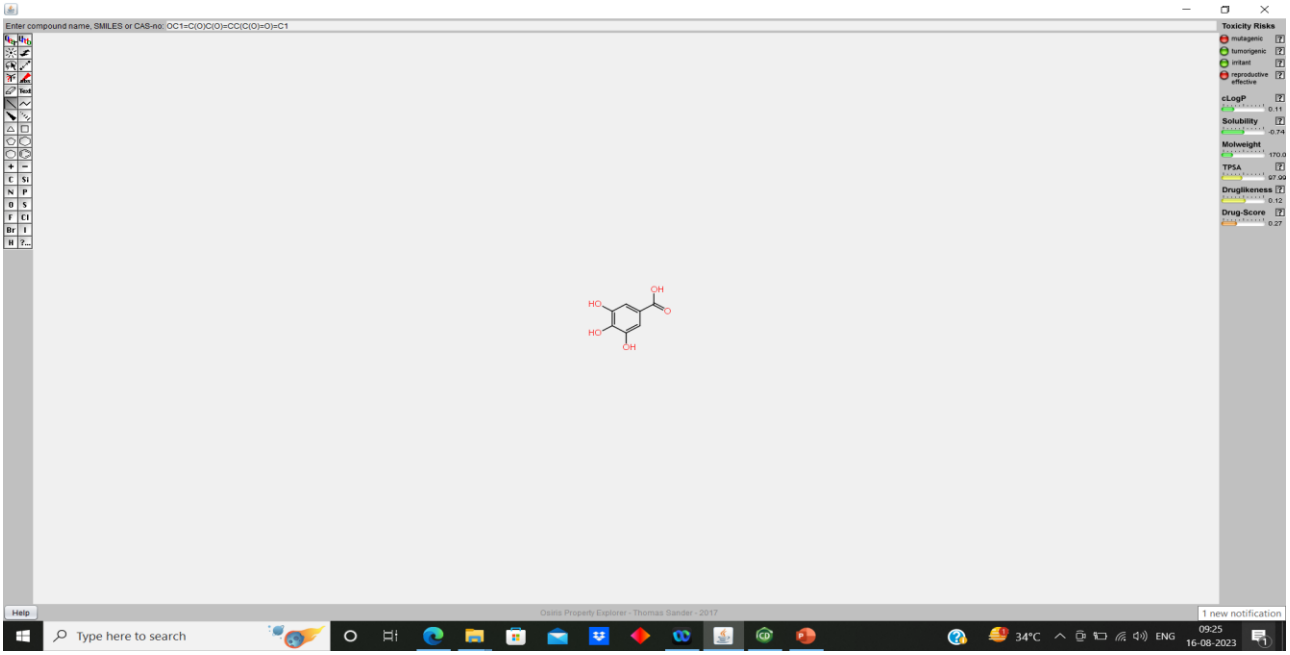


Figure 6: Pharmacokinetic and toxicity profiling of gallic acid

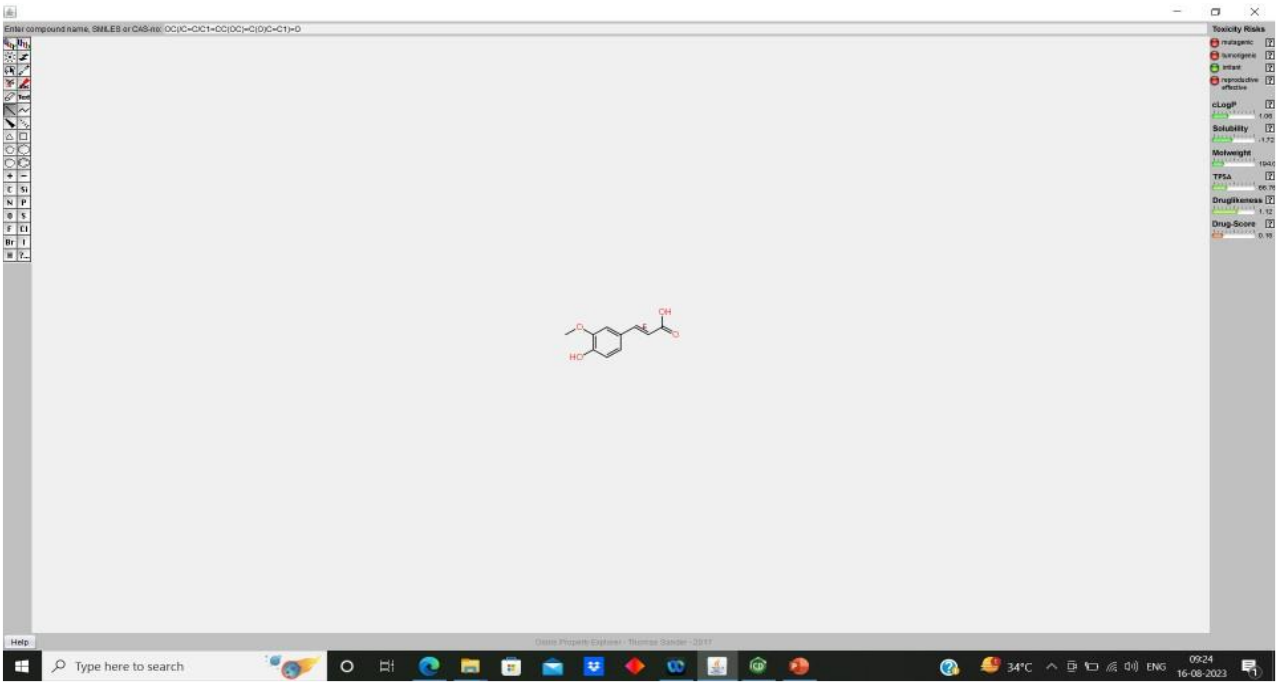


Figure 7: Pharmacokinetic and toxicity profiling of ferulic acid

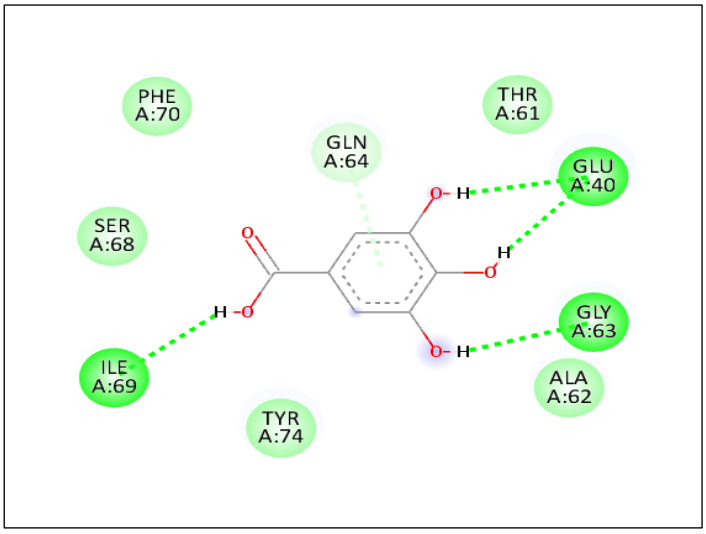


Figure 8: Two-dimensional binding mode of gallic acid within the active site of human mTORC1 receptor

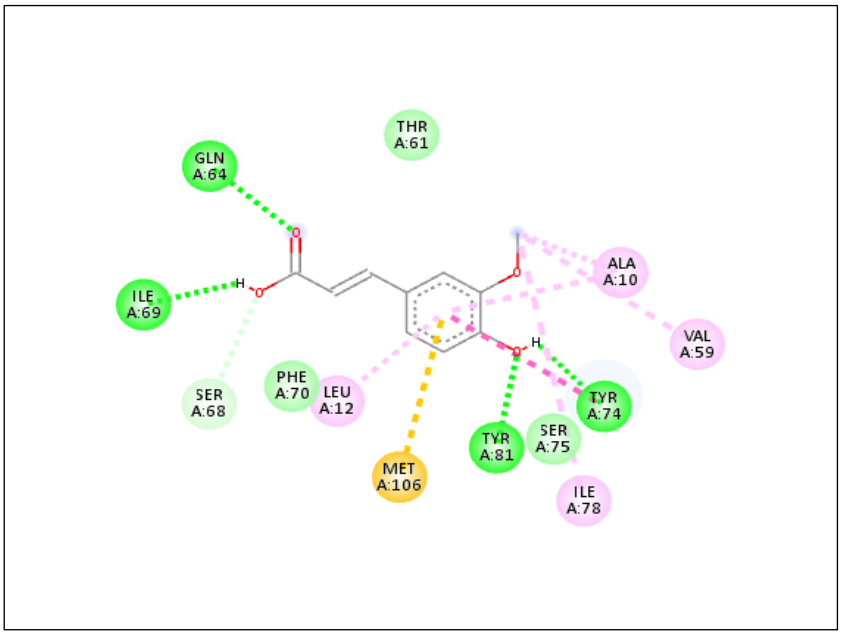


Figure 9: Two-dimensional binding mode of ferulic acid within the active site of human mTORC1 receptor

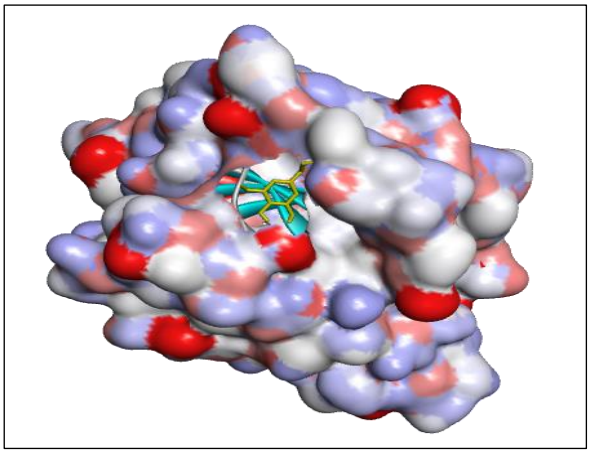


Figure 10: Three-dimensional binding conformation of gallic acid within the active site of human mTORC1 receptor

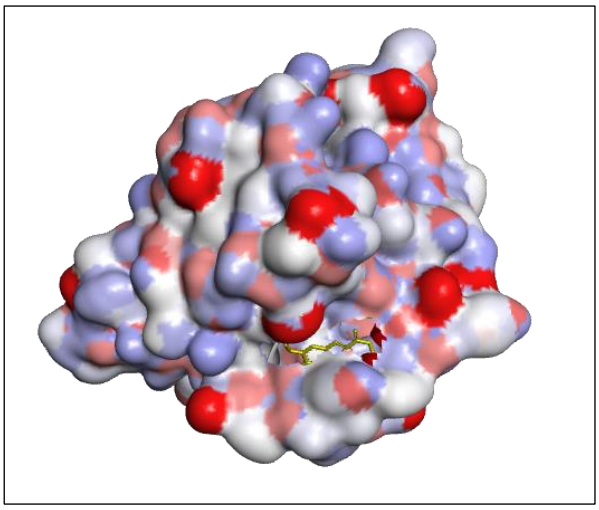


Figure 11: Three-dimensional binding conformation of ferulic acid within the active site of human mTORC1 receptor

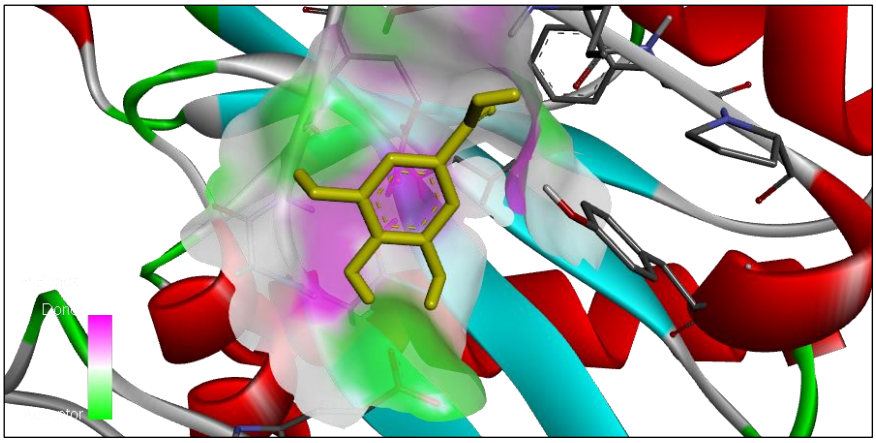


Figure 12: Three-dimensional binding mode of gallic acid within the active site of human mTORC1 receptor

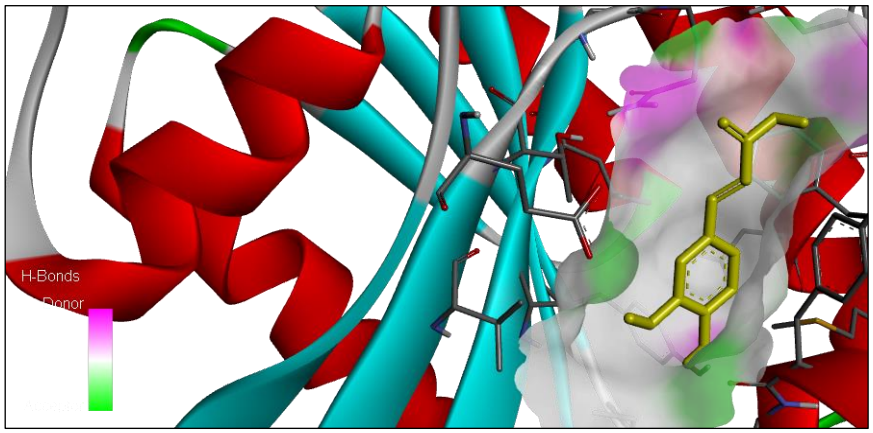
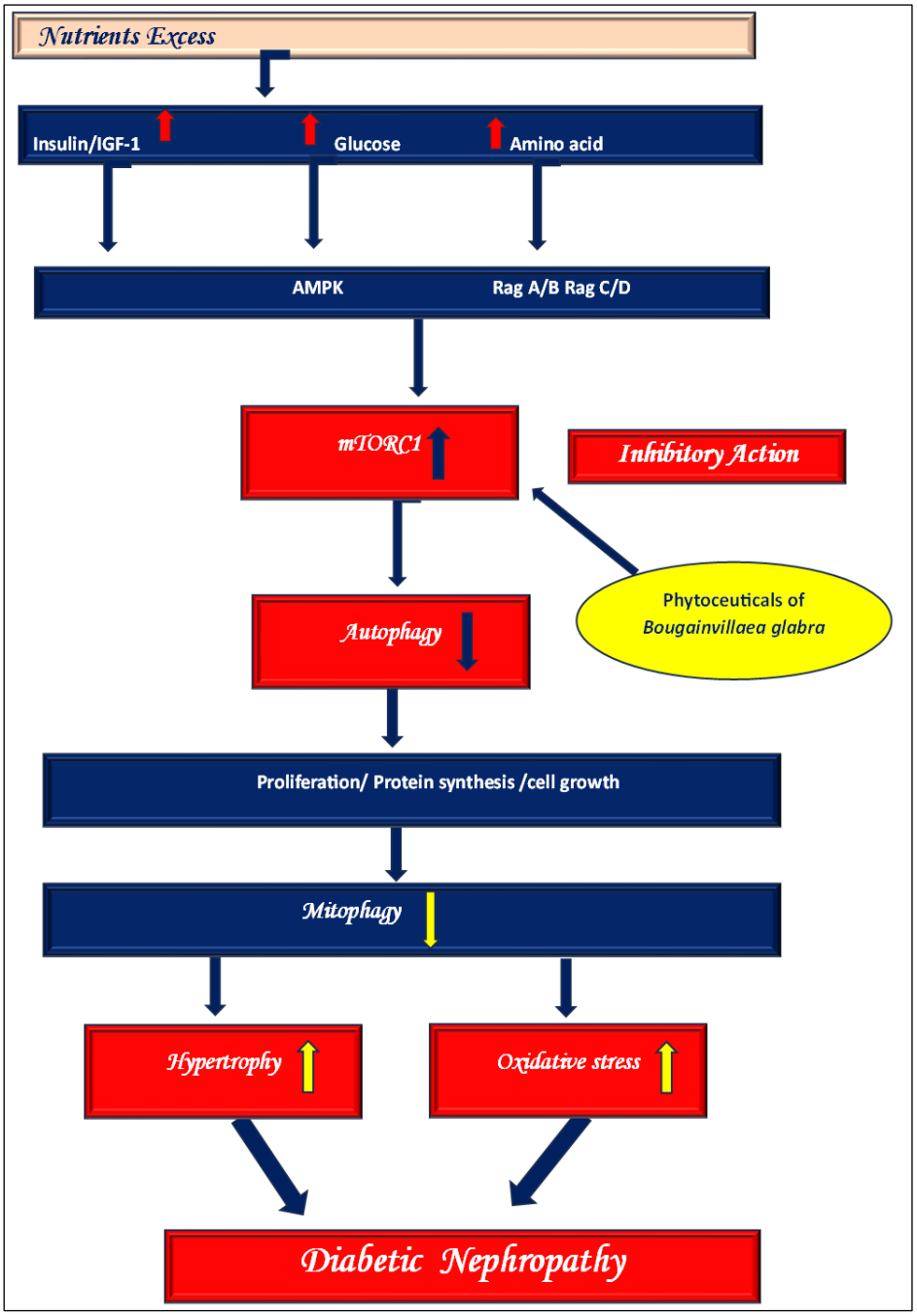


Figure 13: Three-dimensional binding mode of ferulic acid within the active site of human mTORC1 receptor

Divulgence of Investigation

The current investigation concentrated on the phenolic component in Bougainvillae glabra's effectiveness against DN. According to a computational analysis, some phytoceuticals have strong interactions with key ***mTORC1*** protein binding sites and may have inhibitory effects on DN. Additionally, the phenolic compounds found in plants have been shown to have anti-diabetic benefits through a variety of pathways, including activation of the AMPK pathway, inhibition of the enzymes glucosidase and amylase, enhancement of glucose uptake and insulin sensitivity, and activation of PPAR, according to prior research. Additionally, Bougainvillae glabra showed a great deal of promise in

improving renal function in DN patients. Phytoceuticals also have no overt adverse effects, a superior safety profile, and good absorption. Proposed mechanism of action of active phenolic constituents of *Bougainvillae glabra* are shown pictorially as follow:



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