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Exploring the potential therapeutic value of *Solanum lycopersicum L.* phytoconstituents for Parkinson's disease through molecular docking analysis

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Abstract

Parkinson's disease is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the brain, leading to motor and non-motor symptoms. The search for novel therapeutic agents to mitigate the progression of the disease and alleviate its symptoms has led to the exploration of natural compounds. *Solanum lycopersicum L.*, commonly known as tomato, contains various phytoconstituents that have shown promise in neuroprotection and anti-inflammatory properties. This study aims to investigate the potential therapeutic value of *Solanum lycopersicum L.* phytoconstituents for Parkinson's disease through a comprehensive molecular docking analysis. Using state-of-the-art computational techniques, we will evaluate the binding interactions between these phytoconstituents and key protein targets associated with Parkinson's disease. The findings from this research may contribute to the development of new therapeutic strategies and drug candidates for the management of Parkinson's disease.

Keywords: *Solanum lycopersicum L.;* Parkinson's disease*;* Carbidopa*;* Molecular docking*;* Phytoconstituents

1. Introduction

The tomato, *Solanum lycopersicum L.*, is a member of the Solanaceae family and is a night bloomer [1]. It grows well in shaded areas. In the globe, tomatoes rank as the second most valuable vegetable crop. With 4.85 million cultivated acres, it currently produces 182.3 million tons of fruits annually [2]. It is among the crops that are grown and eaten most frequently worldwide. In the world, tomatoes are thought to be the most widely grown and processed crop [3]. The Solanaceae family, which also contains a number of other commercially significant plants, is where it belongs. In India, some of the tomato types with high yields are Arka Rakshak, Pusa 120, Carmello, Vaishali, Rupali, Arka Shrestha, Sioux, and many more. Tomatoes can be compared to Golden and Love apples. Given their low fat content and lack of detrimental cholesterol, tomatoes are regarded as a component of a healthy diet. Tomatoes are a substantial source of several nutrients, including vitamin A, ascorbic acid, potassium, and folate. Tomatoes are rich sources of non-nutritive phytochemicals such as polyphenols (flavonoids, flavanones, and flavones) and carotenoids (lycopene, phytoene, and

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b-carotene). Phytochemicals and minerals like lycopene, potassium, iron, folate, and vitamin C are abundant in tomatoes [4].

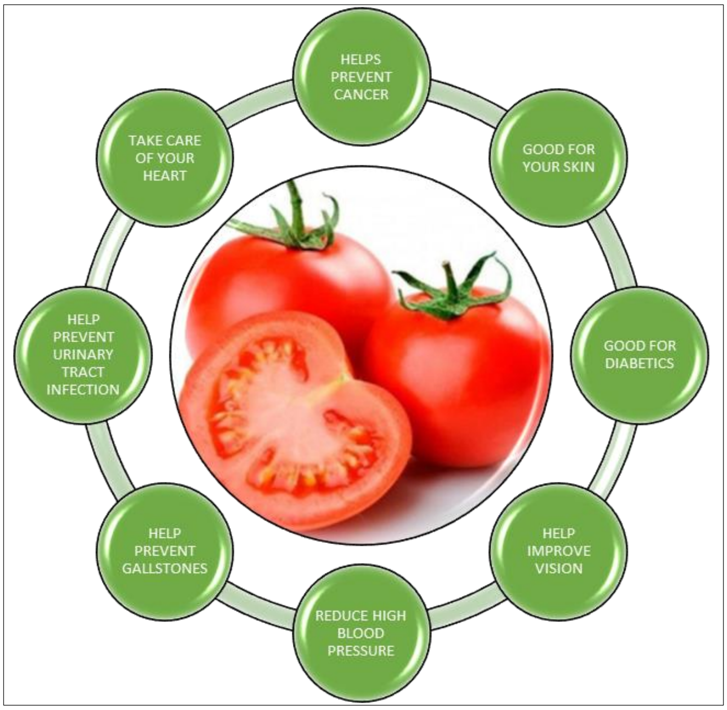


Figure 1 Medicinal benefits of tomato

1.1. Phytochemicals and their bioactivities in tomato

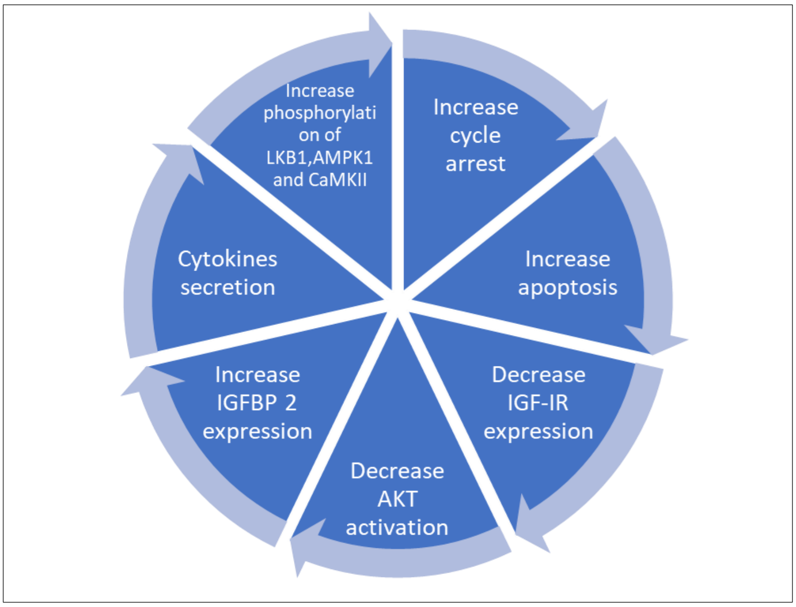
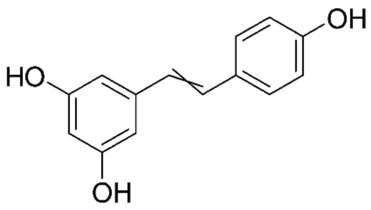
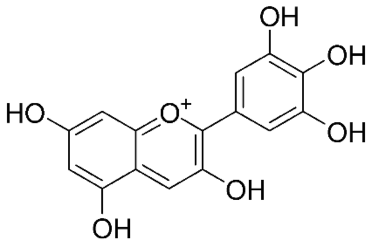
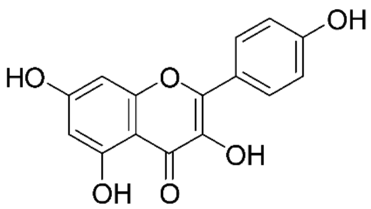
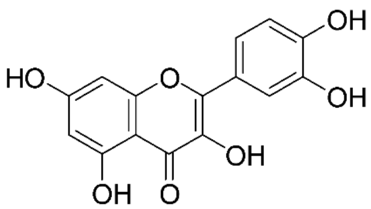
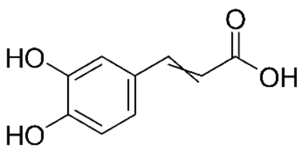
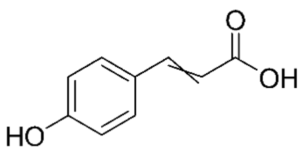
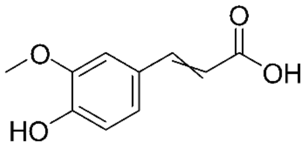
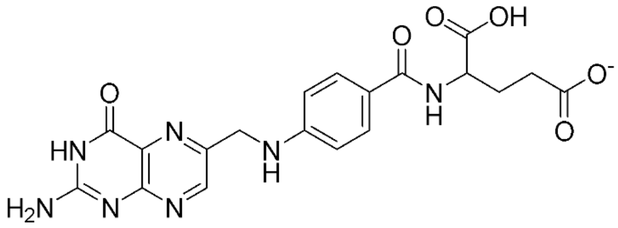
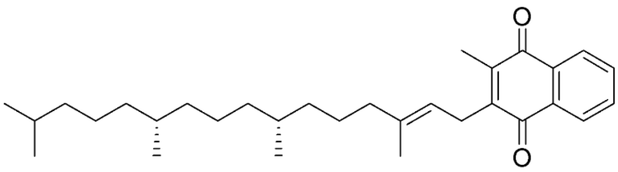
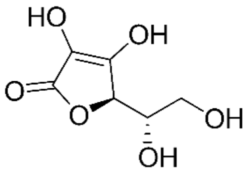
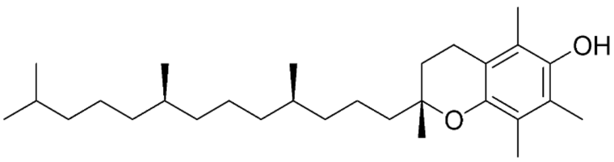


Figure 2 Bioactivities of tomato

Tomatoes are rich in phytochemicals that have anti-inflammatory, anti-mutagenic, anti-carcinogenic, anti-proliferative, anti-oxidative, and anti-atherogenic qualities. Oxidative stress caused by reactive oxygen species (ROS) is the main cause of cancer and CVD. ROS oxidatively destroy essential biological macromolecules, including nucleic acid, lipids, and proteins. Protective effects against ROS are provided by the antioxidant defense system. While polyphenols, carotenoids, vitamin C, and vitamin E are derived from diet, antioxidants like catalases, glutathione peroxidases, and superoxide dismutase are found within human cells [5]. Naturally occurring in tomatoes, lycopene has significant anticancerous and anti-atherogenic qualities. Its singlet-oxygen quenching capability is higher than that of β-carotene and α-tocopherol. By ensnaring reactive oxygen species (ROS), dietary lycopene increases the body's natural lycopene concentration and boosts total antioxidant capacity, thereby mitigating oxidative damage to biological molecules. The bioactivities of tomatoes are depicted in Figure 2 [5].

Table 1 Some phytoconstituents of tomato along with structures and pharmacological activity [6-11].

Class	Phytoconstituents	Pharmacological activity
Stillbenoids	 Resveratrol	Cancer Diabetes Cardiovascular Neurodegenerative Skin
	 Delphinidin	
Flavanoids	 Kaempferol	Cancer Diabetes Cardiovascular Neurodegenerative Skin
	 Quercitin	
Phenolic Acids	 Caffeic acid	Cancer
	 p-Coumaric acid	

	 Ferulic acid	
Vitamin B	 Folate	Atherosclerosis
Vitamin K	 Phylloquinone	Infertility
Vitamin C	 Ascorbic acid	Cancer Diabetes Skin
Vitamin E	 Alpha tocopherol	Cancer Diabetes Cardiovascular Infertility

1.2. Pharmacological actions of Tomato

Tomatoes have recently come to be recognized as having the ability to prevent certain human diseases. The reason for this is that carotenoids, particularly lycopene, seem to be involved in the prevention of cancer, reduction of cardiovascular risk, and slowing down the aging process of cells [12]. The high levels of lycopene and β-carotenes in tomatoes act as antioxidants and scavengers of free radicals, making them beneficial for health by lowering the risk of cancer and cardiovascular diseases [13]. However, due to the high concentration of different allergenic proteins, eating tomatoes can result in allergic reactions [14]. Increased LDL oxidation resistance and decreased LDL cholesterol levels can be achieved through diets high in tomato products [15]. Tomato consumption during the meal reduced postprandial lipemia-induced oxidative stress and associated inflammatory reactions [14]. In order to keep DNA stable, tomatoes have also been very important. Lyc-O-Mato, a tomato-based beverage, can significantly (about 42%) reduce DNA damage to lymphocytes under oxidative stress on a daily basis [16]. Consuming tomatoes for two to three days as opposed to zero day has been linked to a significant decrease in mortality (48%) and a lower risk of death from diarrhea [18].

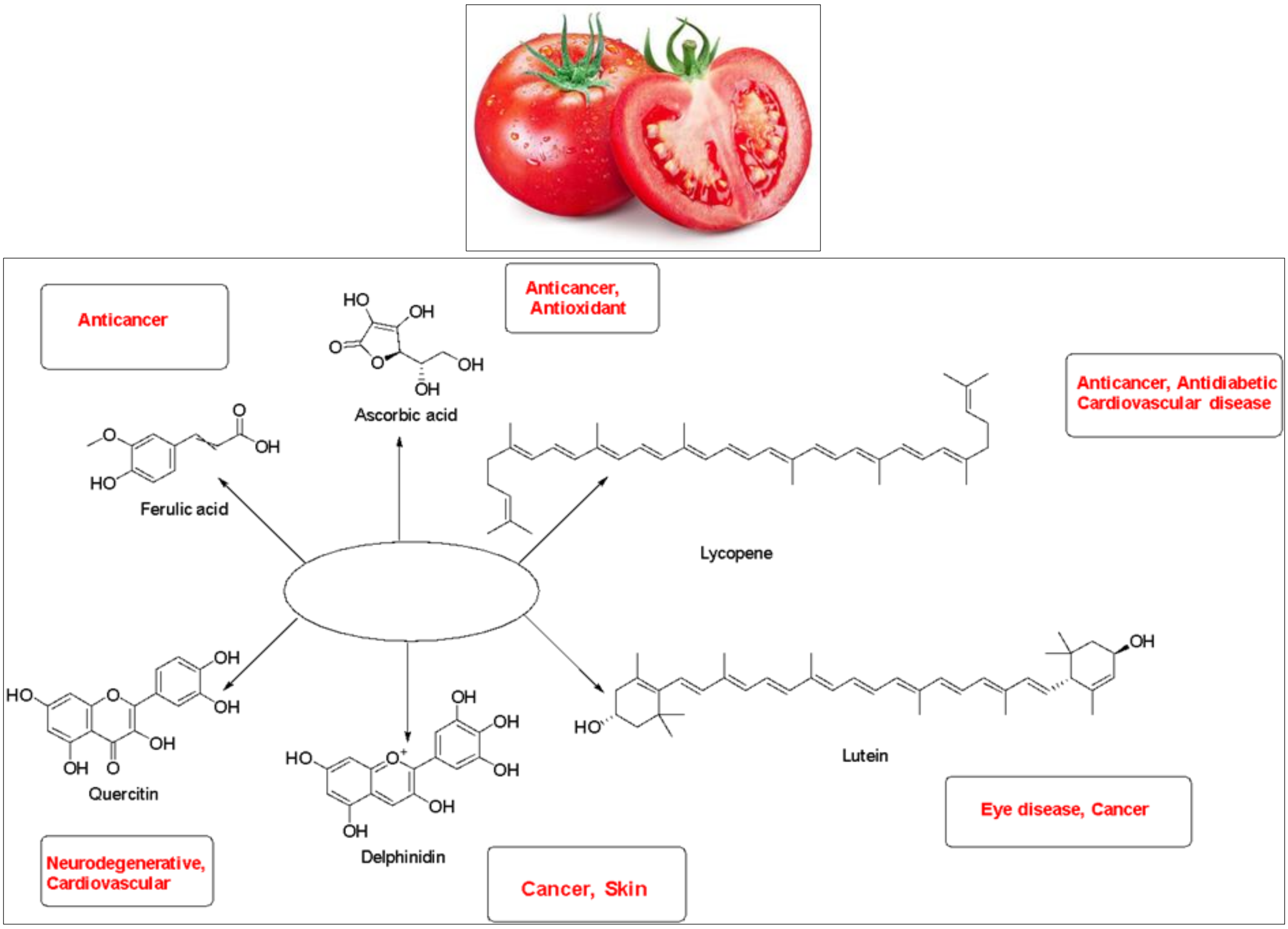


Figure 3 Major Phytoconstituents and their pharmacological activities

1.3. Parkinson Disease

It results from a combination of genetic and environmental factors, and manifests with a broad range of symptoms. The classical motor symptoms of Parkinson’s disease have been recognised as prominent com ponents of the disease. Motor features in patients with Parkinson’s disease are heterogeneous. Non-motor features are also frequently present in Parkinson’s disease before the onset of the classical motor symptoms [19]. Diagnosis of Parkinson disease is based on history and examination. History can include prodromal features (eg. rapid eye movement, sleep behaviour disorder, hyposmia, constipation), characteristic movement difficulty (eg. tremor, stiffness, slowness), and psychological or cognitive problems (eg. cognitive decline, depression, anxiety) [22]. Neurological disorders like Parkinson's disease are common and complex [19]. Facing 2-3% of the population over 65, it is the second most prevalent neurodegenerative disorder [20]. Parkinson's disease is a neurodegenerative illness characterized by the early and prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [19] or the accumulation of Lewy bodies, which are -synuclein misfolded and accumulate in multiple systems of Parkinson disease patients [21]. As a result, there is a dopamine deficit in the basal ganglia, which can cause a movement disorder with multiple non-motor symptoms or classical parkinsonian motor symptoms. Not only dopamine but also parts of the nervous system outside the basal ganglia are affected by Parkinson's disease.

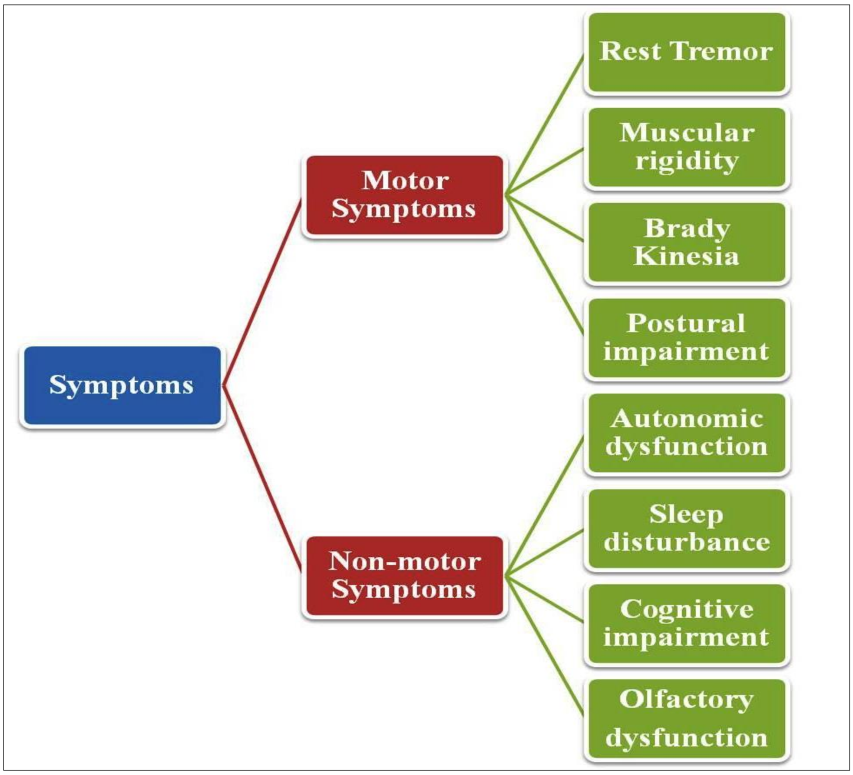


Figure 4 Motor and non-motor symptoms of Parkinson's disease

Gender, ethnicity, age, genetic variation, and environmental factors (such as pesticide exposure and prior head injuries) are among the numerous risk factors that contribute to Parkinson disease. Rural residence and beta-blocker use Utilizing well water for drinking in agriculture) [19]. The cornerstone of symptomatic treatment for Parkinson disease's motor symptoms is dopaminergic medication. Dopamine agonists and monoamine oxidase B inhibitors were made available after levodopa was the first medication to treat Parkinson disease symptoms. It is possible for drugs that block dopamine receptors to cause neuroleptic malignant syndrome, parkinsonism, or a significant worsening of motor symptoms in patients with Parkinson disease. These comprise neuroleptics like promethazine, chlorpromazine, thioridazine, and haloperidol, among others [21]. There are no pharmacological treatments that stop or slow the progression of Parkinson disease [23]. In a recent phase 2 randomized clinical trial, the high-intensity exercise group experienced a significantly smaller decline in motor function compared to the usual care group in patients with Parkinson disease that had recently started [24] Although there is currently no treatment to stop or slow down the progression of Parkinson's disease, a number of promising approaches are being investigated for their ability to modify the disease in light of recent discoveries regarding the genetic causes and mechanisms of neuronal death [21]. The clinical identification of therapeutic agents capable of ameliorating or delaying the detrimental processes linked to Parkinson's disease (PD) is imperative. Examining the potential role of natural products that might interfere with Parkinson's disease pathology is one such paradigm [25]. The discovery of particular molecular or pharmacological effects in natural products is likely to aid in the creation of neuroprotective agents against Parkinson's disease (PD) [26]. Rich in lycopene, Lycopersicon esculentum L., or tomato, is widely recognized for its edible fruit. A reduced DA loss in an MPTP-induced Parkinson's disease model was correlated with pretreatment with a diet containing lyophilized tomato powder [27]. Bioactive tomato constituents such as polyphenols and carotenoids, of which lycopene (LYC) is particularly effective at reducing markers of oxidative stress, and in cell cultures and animal models, these compounds appear to have a protective modulator role on the pathogenetic mechanisms, cognitive symptoms, and behavioral manifestations of these diseases [28]. Certain drugs, like Olaparib, have demonstrated their effectiveness in treating cancer. These drugs, known for their antioxidant and anti-malignant properties, hold potential for also addressing Parkinson's disease, drawing on established principles in conventional medicine [29]. Additionally, a comprehensive review manuscript explores the use of herbal remedies and conventional methods in managing conjunctivitis among atypical populations [30]. It's worth noting that recent research has already conducted in-silico screening for epilepsy treatment by identifying phytochemical components in Cannabis sativa L phytoconstituents [32]. Furthermore, there's research on phyto-pharmacognostic approaches applied to treat hypogonadism, utilizing herbal plants along with a screening of their phytochemical properties [31].

2. Material and Methods

2.1. IN-SILICO/ MOLECULAR DOCKING STUDY

After review literature from various review and research manuscript selected compounds were selected and prepared chemical structures as a ligand of phytoconstituents from *Solanum lycopersicum L.*, including chalcone, myricetin, quercitin, 13-cis-retinoic acid, retinoil, naringenin, and kaempferol, were used for virtual derivative screening in conjunction with standard medication called carbidopa as shown in Table 2. ChemDraw 19.1 was used to draw them. The Schrodinger suite version 13.1 was used for molecular docking.

2.2. Protein preparation

Chlorogenic acid, Myricetin, Quercitin, 13-cis-retinoic acid, Retinol, Naringenin, Kaempferol, and Chalcone transcriptional regulation (PDB Id: 2V5Z) were selected from the Protein Data Bank for the molecular docking study of a given data set of *Solanum lycopersicum L.* phytoconstituents, as indicated in Table 2. For immediate use in molecular modeling calculations, the standard structure file downloaded from the PDB is unsuitable. A typical PDB structure file contains cofactors, metal ions, water molecules, and co-crystallized ligands, among other things. Before producing protein, the protein preparation wizard optimized, reduced, and preprocessed it. The final result is a refined, hydrogenated ligand and ligand-receptor complex structure that can be used with different Schrodinger modules [33].

2.3. Ligand Preparation

The ligands are ready for the best docking results with the help of the Maestro v 13.1 LigPrep module. It is necessary that the docked structures accurately reflect the actual ligand structures as they would be found in a complex of proteins and ligands. The following Glide docking software requirements must thus be met by the structures. It needs to be three dimensions. The other geometric parameters need to be adjusted beforehand because Glide only adjusts the ligand's internal torsional coordinates. Without any covalent receptor attachments or additional components like solvent molecules or counter ions, each of them must be a single molecule. They have to be filled with hydrogen (valences). The pH levels of the body are approximately 7, so they must be appropriately protonated [34, 35].

2.4. Molecular docking

The maestro v 13.1 ligand docking module was used for docking after the glide grid zip file was created and the ligands were ready. Chlorogenic acid, Myricetin, Quercitin, 13-cis-retinoic acid, Retinol, Naringenin, Kaempferol, and Chalcone are among the phytoconstituents of *Solanum lycopersicum L.* that undergo more precise molecular docking through the use of the XP module. As precision increases, the size of the data collection shrinks. The docking score, glide energy, and glide model value of the XP parameters were estimated in Maestro v 13.1 [37, 38]. Chalcone, Kaempferol, Myricetin, Quercitin, 13-cis-retinoic acid, Retinol, Naringenin, and Chlorogenic acid undergo In-silico screening analysis as a phytochemical/compound/ligand of *Solanum lycopersicum L.* Afterwards, we generate a collection of nine chemical structures also known as Ligand, in which comprising of eight phytochemicals found in *Solanum lycopersicum L.* and one common drug, carbidopa. From there, we choose all of the phytochemical docked score of *Solanum lycopersicum L.* binding at receptor (2V5Z) displayed in Figure No. 5. As can be seen in Table No. 2 and Figure. No. 6–14, which show a 2D and 3D ligand-protein interaction, respectively, all eight of *Solanum lycopersicum L.*'s markers show higher docking scores and glide energies when compared to standard anti-parkinson drugs like Carbidopa as shown in Table No. 2. Additionally, studies have already been conducted to evaluate the viability and potential of insilico analysis in predicting the medications derived from medicinal plants to treat a variety of illnesses and disorders, including epilepsy [32], monkeypox [40], traits to identify the genotypes of the promising mango [42], in-silico for some conventional drugs like insilico design of a novel silver metal ciprofloxacin compound [43], and synthetic and insilico design of gallic acid derivatives article that shows development and validation of antioxidant activity via this method. Molecular docking simulation [44], as well as the use of Elettaria cardamomum phytoconstitutents in the treatment of cardiovascular disease [45].Additionally, some studies demonstrate the chemical constituents in ganoderma mushrooms are beneficial in the management of malignant cells [47], and one study uses in-silico screening to demonstrate the beneficial effects of phytoconstituents of the medicinal plant Holoptelea integrifolia on the SARS-CoV-2 virus [48]. Other manuscripts provide strong evidence of antimicrobial activity by synthetic and biological therapeutic activity of some novel chalcones derivatives [46]. Reproductive failure also a majaor cause so that implantation failure as shown in article [49]. Tomatoes have a great deal of potential for preventing and/or treating a number of chronic degenerative diseases, as evidenced by the bioactive components' demonstrated anti-inflammatory, antidiabetic, antioxidant, and other health-promoting properties. Strong antioxidant qualities of two key tomato active components, lycopene and β-carotene, have been related to numerous health advantages, including prevention of heart disease and cancer. Additionally, they help to stop cataracts from developing. The body benefits from the water content and dietary fibres in addition to improved hydration, regular bowel movements, decreased constipation, improved obesity through weight loss, and prevention of colon cancer. Tomatoes are active ingredients for the creation of functional foods because of all of their immune-stimulating properties. Tomatoes are therefore a great source of nutritional value from food and can help prevent sickness [50]. In the present study, it has been demonstrated that synthetic and particularly molecular docking analysis yields novel phytochemical discoveries, as demonstrated in this research manuscript based on molecular docking analysis of *Solanum lycopersicum L.* phytoconstituents for the Management of Parkinson's disease.

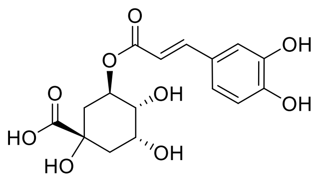
3. Result and Discussion

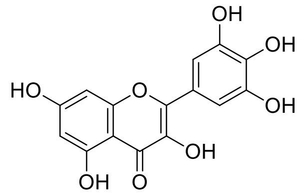
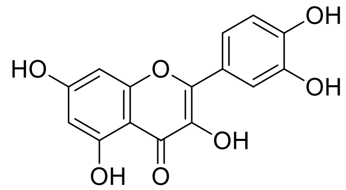
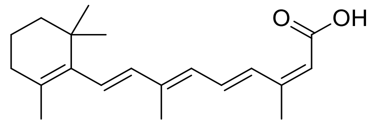
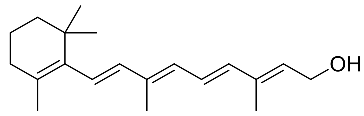
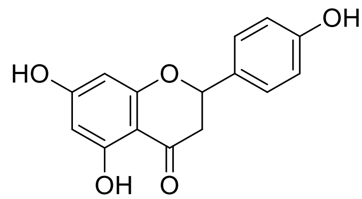
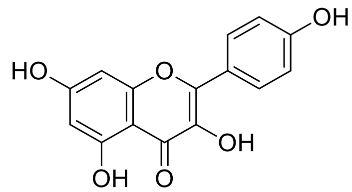
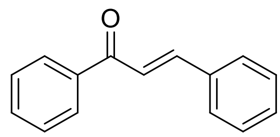
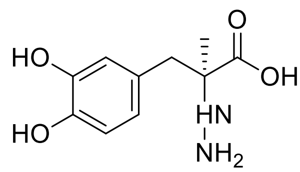
2V5Z: Structure of human MAO B in complex with the selective inhibitor safinamide [39].

- **Classification:** OXIDOREDUCTASE
- **Organism(s):** Homo sapiens
- **Expression System:** Komagataella pastoris
- **Mutation(s):** No
- **Membrane Protein:** Yes

Figure 5 3D- Structure of protein (2V5Z)

Table 3 *Solanum lycopersicum L.* phytoconstituents docking screening result in comparison to standard anti-parkinson drugs.

S.No	Name of Compounds	Chemical Structure	Docking score (PDB ID: 2V5Z)	Molecular Weight	cLogP
	Chlorogenic acid		-10.97 *KJ/mol*	354.31	-1.879

	Myricetin		-10.883 *KJ/mol*	318.24	0.836
	Quercitin		-10.593 *KJ/mol*	302.24	1.503
	13-cis-retinoic acid		-10.289 *KJ/mol*	300.44	6.744
	Retinol		-10 *KJ/mol*	286.45	6.403
	Naringenin		-9.766 *KJ/mol*	272.25	2.444
	Kaempferol		-9.538 *KJ/mol*	286.24	2.099
	Chalcone		-9.286 *KJ/mol*	208.26	3.624
	Carbidopa (Standard drug)		-8.404 *KJ/mol*	226.23	-0.444

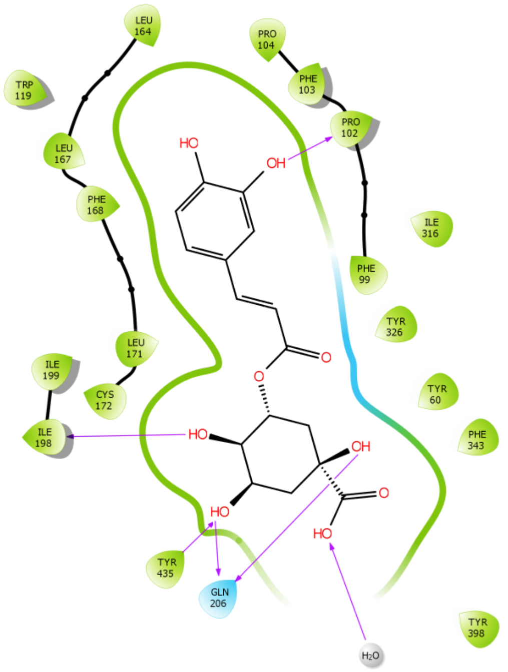


Figure 6 Chlorogenic acid 2D diagrams of docked conformation compound

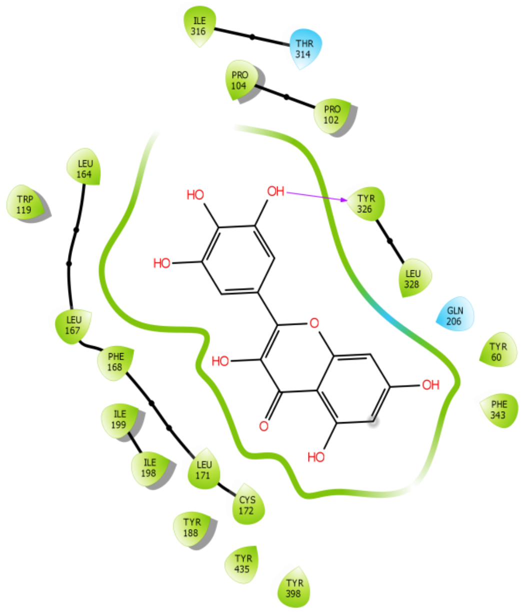


Figure 7 Myricetin 2D diagrams of docked conformation compound

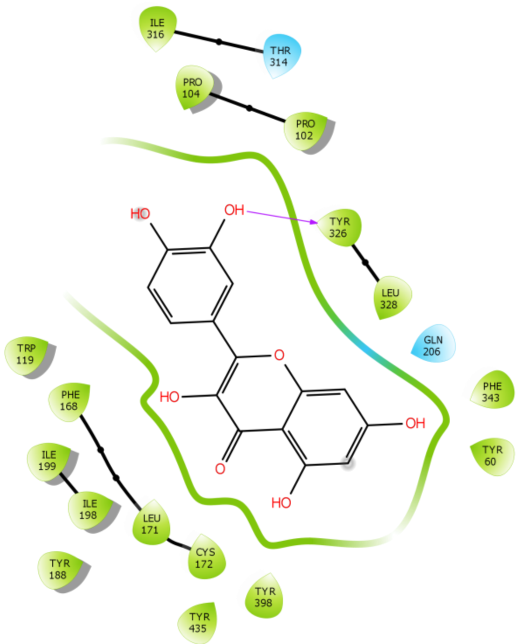


Figure 8 Quercitin 2D diagrams of docked conformation compound

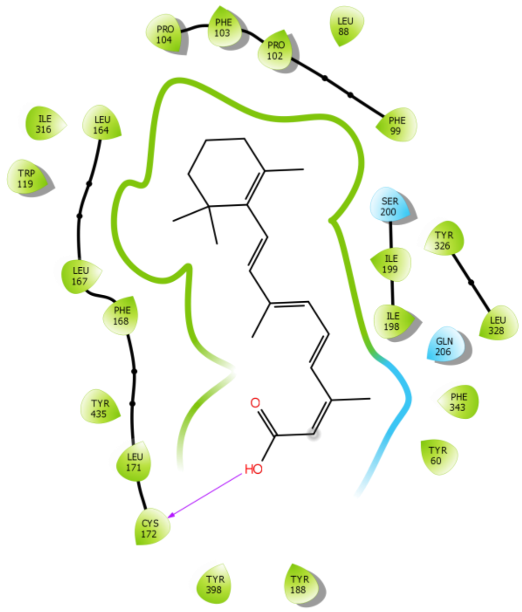


Figure 9 13-cis-retinoic acid 2D diagrams of docked conformation compound

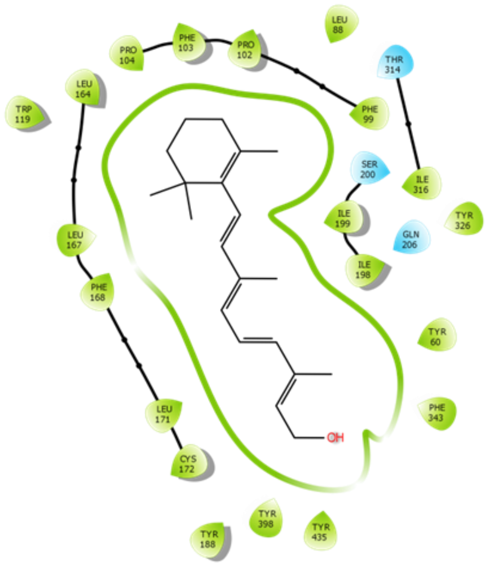


Figure 10 Retinol 2D diagrams of docked conformation compound

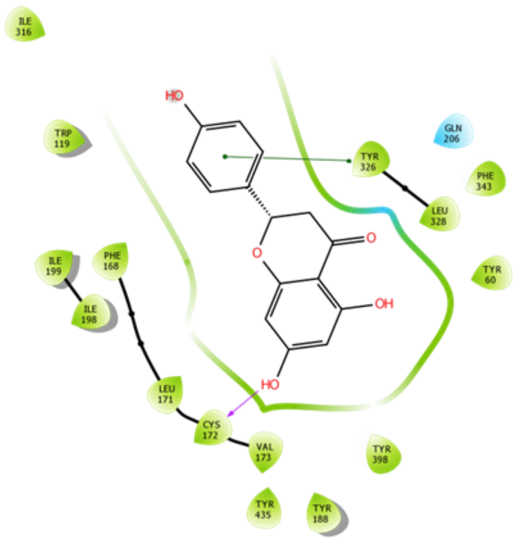


Figure 11 Naringenin 2D diagrams of docked conformation compound

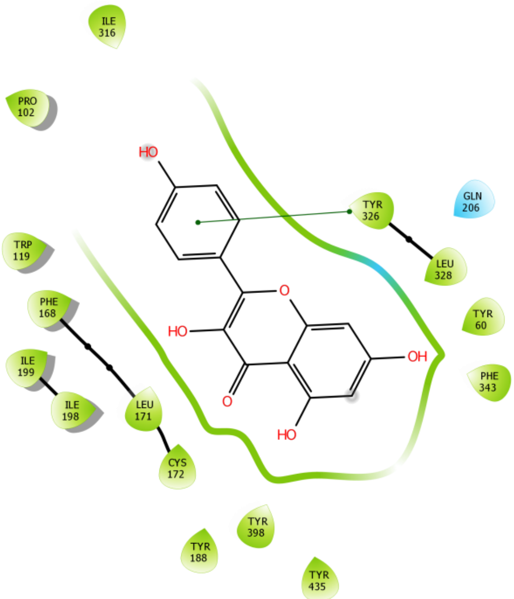


Figure 12 Kaempferol 2D diagrams of docked conformation compound

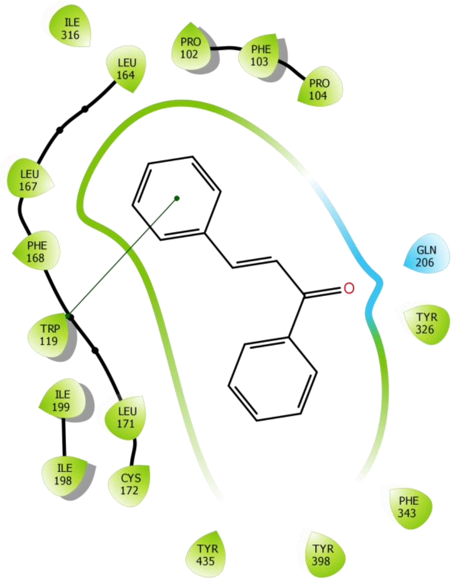


Figure 13 Chalcone 2D diagrams of docked conformation compound

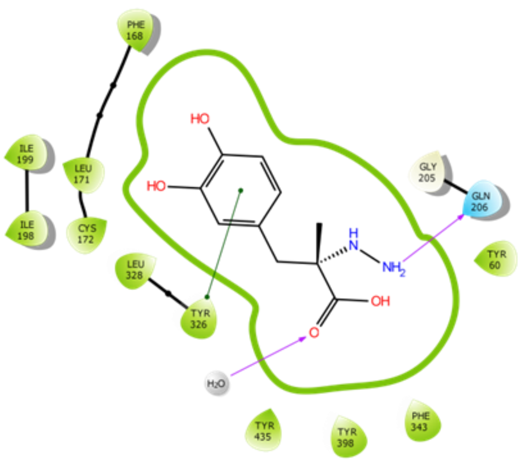


Figure 14 Carbidopa 2D diagrams of docked conformation compound

4. Conclusion

In our study, the foundational methodology is computational molecular docking, and it is of paramount importance to ascertain the validity of the scientific tool, Maestro 12.8, utilized for our molecular docking investigations. Our research outcomes underscore the robust and effective properties exhibited by specific phytoconstituents, particularly in the context of addressing neurodegenerative diseases and disorders, with a specific focus on Parkinson's disease. Our research study is centered on the composition of phytoconstituents naturally found in the seeds of *Solanum lycopersicum L*., including Chlorogenic acid, Myricetin, Quercitin, 13-cis-retinoic acid, Retinol, Naringenin, Kaempferol, and Chalcone. Moreover, we conducted an additional in silico study, utilizing the Protein Data Bank identifier (PDB ID: 2V5Z), to assess the potential of these *Solanum lycopersicum L*. phytoconstituents. When compared to a standard drug like Carbidopa, which exhibited a binding energy of (-8.404 KJ/mol) furthermore phytoconstituents utilized in this study demonstrated superior docking scores and reduced glide energies, with Chlorogenic acid emerging as the most promising with an affinity of (-10.97 KJ/mol) when compared to standard drug like Carbidopa. This in silico analysis highlights the substantial potential of *Solanum lycopersicum L*. phytoconstituents in addressing a spectrum of neurodegenerative diseases and disorders. It positions these natural compounds as valuable candidates for the development of novel anti-Parkinson drugs and suggests their potential utility in the treatment of various psychotic disorders and central nervous system (CNS) diseases in the future. In conclusion, our research findings underscore the potency of *Solanum lycopersicum L*. phytoconstituents, with a specific emphasis on Chlorogenic acid, as demonstrated through in silico studies shown in Table 2. This opens doors for their potential application as pivotal components in the creation of innovative treatments for neurodegenerative diseases, including Parkinson's disease and other CNS disorders. Subsequent research and clinical investigations are warranted to effectively harness their therapeutic potential.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare there is no conflict of interest in this study.

Statement of informed consent

Informed consent was obtained from all individual participants.

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