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Investigation of *Scutellaria baicalensis* for Potential Neuroprotective Effect on the Treatment of Parkinson's Disease

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Abstract: Parkinson's disease (PD) is a progressive neurological disorder that lacks adequate treatment, and researchers have focused on rescuing or delaying neurodegeneration in PD. *Scutellaria baicalensis* has shown promising results in reducing oxidative stress and demonstrating a neuroprotective effect on PD animal models. However, the exact mechanism by which *S. baicalensis* treats PD is not yet fully understood. To investigate the potential molecular mechanisms underlying *S. baicalensis* antiparkinsonian efficacy, this study used network pharmacology. Open-source datasets were used to compile phytoconstituents, and virtual screening was conducted to identify hit phytoconstituents that target proteins involved in PD development. The drug-likeness value, ADMET analyses, and negative consequences of the phytochemical constituent were evaluated. Regulating pathways were anticipated with the Kyoto Encyclopedia of Genes (KEGG) record. 7 phytochemical constituents from *S. baicalensis* were found to alter the activity of proteins involved in PD occurrence, with 5-hydroxy-7,8-dimethoxyflavones having the highest docking result of -8.337 kcal/mol and active amino acids SER 91, as well as the drug-likeness value at the highest edge points. Through the networking of phytoconstituents, genes, and pathways, the study revealed that the neuroactive ligand-receptor interaction route was tightly synchronized.

Keywords: Parkinson's disease; neuroactivity; computational analysis; *Scutellaria baicalensis;* phytoconstituents

1. Introduction

PD is characterized by the loss of dopaminergic neurons in the substantia nigra (SN) of the brain. Therapies for PD involve the use of synthetic molecules. While these synthetic compounds are effective in protecting neurons, they may cause severe adverse effects, for example, psychosis and hallucinations. Additionally, the use of synthetic molecules can generate reactive oxygen species (ROS), which can cause mitochondrial dysfunction [1-2]. PD

is a genetic variant disorder, which indicates that the disease's progression involves multiple genes [3]. Altering a particular protein's role can activate multiple pathways, leading to synergism with the pathological pathway of PD. This highlights the involvement of several genes cooperating to trigger a particular response. To address the pathology of PD, antiparkinsonian medications target specific targets from different drug target approaches. However, a focal point "selective drug target approach" may cause several pharmacological consequences [4]. Due to the complex and progressive nature of PD, a "multiple protein drug approach" using lower dose concentrations may be recommended to achieve a mutual connection. Plant-based remedies have demonstrated diverse neuroprotective properties, along with the capacity to extend dopamine levels in the SN with minimal adverse effects [5]. While many plant-extract treatments have shown promise as prolonged neuroprotective agents, the efficacy of some effective plant extracts in managing PD lacks scientific evidence. *S. baicalensis* is a Chinese traditional medicine known as “huangqin” and it is a member of the Lamiaceae family that possesses various pharmacological activities to manage diabetes, cancer, and neurological disorders [6,7]. These herbal plants actually contain flavonoids, which have exhibited potent antiparkinsonian effects in many *in vivo* studies of PD [8]. The crystalline structure of the dopaminergic receptor D4 bound to the subtype-selective ligand L745870 can be found in the database under the PDB ID-6IQL. The brain's mesolimbic system is a region that coordinates dopaminergic and complex behavior through dopaminergic receptor D4 (DRD4), a G protein-coupled receptor (GPCR), to transmit signals between neurons. Overall, the DRD4 gene's significance lies in its function in controlling the brain's dopaminergic systems and remuneration pathways, which may have implications for a range of neurological disorders as well as behavior in PD [5].

Although the mechanism by which *S. baicalensis* exerts its therapeutic effects in PD is not fully understood, it has been demonstrated to effectively alleviate inflammatory conditions, oxidative stress, and mitochondrial failure. Therefore, the objective of this research is to determine the active components of *S. baicalensis* that contribute to its efficacy, identify the various targets involved in PD progression, and provide insight into the underlying mechanisms through the network pharmacological strategy.

2. Materials and Methods

2.1. Identification of phytochemical constituents and proteins involve in PD.

The bioactive phytochemical constituents of *S. baicalensis* were collected from written articles and scientific papers. The database contains important information such as SMILES, types, and PubChem CIDs for each phytoconstituent to ensure that there were no duplicates; any phytoconstituents that appeared more than once in the dataset were removed (https://pubchem.ncbi.nlm.nih..gov/) [9-10]. Next, the various plant-derived compounds were searched in the Binding Database, and any targets with a similarity percentage between 70-90 percent were compiled into a single document [11]. Then, the Therapeutic Targeted Database index was examined to determine sites that were relevant to the course of PD. Gene IDs for these targeted receptor were acquired from the UniProt database [12]. The molecular structures of the seven collected phytochemicals have been included in the supplementary file (Fig. S1) for reference.

2.2. Drug-likness and ADMET analysis profile of the phytochemical constituents.

Druglikness score was estimated for the phytochemical constituents utilizing the "Lipinski rule of Five approaches" in MolSoft (https://www..molsoft.com/). ADMET study profile of the phytochemical constituents was carried out by using admetSAR2.0 (http://lmmd.ecust.edu.cn/admetsar2) [13,14].

2.3. Detection of adverse effects.

The SMILES of the phytochemical constituents were entered into the ADVERpred database (http://www.way2drug.com/adverpread/) to predict any potential adverse effects[15]. The probable activity (Pa) and probable inactivity (Pi) values were examined, and a threshold of 0.8 was set to determine whether a phytoconstituent's Pa value was greater than its Pi value. If the Pa count exceeded the Pi value by a factor of 0.8 or more, then the potential for side effects of the phytoconstituent was considered [16,17].

2.4. Recognition of protein pathways and interpretation of network.

The study utilized the STRING database (https://string-db.org/) to explore the number of proteins involved with PD. Additionally, the KEGG pathway database indexed (https://www.genome.jp/kegg/) was employed to ensure the pathways and proteins affected by PD. The obtained pathways are available in Table S1 of the supplementary file. By Utilizing Cytoscape 3.7.2, a network was constructed for the targeted pathway, proteins, and phytochemicals. The network was analyzed by counting the nodes and edges, with the heavily affected pathways and proteins possessing the highest number of nodes with connections [18,19].

2.5. Docking studies.

To perform molecular docking, the Schrodinger Suite 2022 was utilized. The ligand creator Maestro tool was used to create the 3-dimensional structure of 5-hydroxy-7,8-dimethoxyflavones, which was prepared at a neutral pH using the LigPrep module. Via the use of the Epik module and the OPLS3 force field, the ligand's overall energy level was brought down [20]. The protein database (https://www.rcsb.org/) was accessed to obtain the PDB ID: 6IQL, which represents a crystallized DRD4 dopaminergic receptor connected to L745870. The protein was constructed using a workflow tool for protein creation, and any missing heteroatoms or amino acids were included in the finished version. The glide component was used to build the grid box, and high-precision docking was accomplished using the ligand docking module in the Schrodinger Suite 2022 glide module [21]. Finally, the pose viewer was utilized to analyze the ligand-receptor associations and docking values.

3. Results

3.1. Collection of phytochemical constituents and proteins involved in PD.

Accessible sources and literature revealed that *S. baicalensis* contains 52 phytoconstituents. Among them, 7 flavones were identified to modulate PD proteins, which are mainly membrane proteins of cells. Table 1 summarizes these flavones and their effects on PD proteins.

Table 1. Phytochemical constituents and altered receptors of *S. baicalensis*.

Name of Compounds	Chemical Class	PubChem ID	Name of Targeted Proteins
Baicalein (5,6,7-trihydroxyflavone)	Trihydroxy-flavones	5281605	DRD4, SNCA, HTR2A, PPARG, ESR2
Wogonin (5,7-dihydroxy-8-methoxyflavone)	Dihydroxy-methoxy-flavones	5281703	ESR2, AKR1B1, PPARG, OPRM1, NTRK2, MKNK2, HTR2A
5-hydroxy-7,8-dimethoxyflavone	Dimethoxy flavones	188316	HTR2A, HTR1A, SNCA, PPARG, MAOA, ALOX5, DRD4, ESR1, IGF1R, OPMR1, SYN1
Norwogonin (5,7,8-trihydroxyflavone)	Trihydroxy-flavones	5281674	ADORA1, HTR2A, DRD4, SNCA
Salvigenin (5-hydroxy-6,7,4'-trimethoxyflavone)	Hydroxy-flavones	161271	HTR2A, FLT1, ADRA2A, SNCA, PPARG
5,7,2',3'-Tetrahydroxyflavones	Tetrahydroxy-flavone	5321864	SNCA, NTRK2, APP, PPARG
Dihydro-oroxylin A (5,7-Dihydroxy-6-methoxyflavanone)	Flavanones	177032	PPARG, HTR1A, HTR2A, ESRRG

3.2. Potential negative impacts, Drug-like properties of phytochemical constituents, and ADMET analysis.

It is important to evaluate the safety and efficacy of phytoconstituents' potential adverse effects, drug-likeness, and pharmacokinetic properties. Therefore, an analysis was conducted to examine these aspects using ADMET (absorption, distribution, metabolism, excretion, and toxicity) study. The ADMET study provided insights into the pharmacokinetic properties of the phytoconstituents, including their bioavailability, half-life, and potential toxicity. Additionally, the drug-likeness of the phytoconstituents was evaluated to determine their potential as therapeutic agents.

Furthermore, the ADMET analysis also revealed possible adverse effects of the phytoconstituents, including toxicity to the liver and kidneys and possible interactions with other medications. These findings suggest that further investigation is necessary to determine the safety and efficacy of the phytoconstituents for use as therapeutic agents.

The potential negative impacts of all seven phytoconstituents were evaluated, and the results indicated that six of them may have hepatotoxicity as a possible side effect. In addition, one of the phytoconstituents, 5-Hydroxy-7,8-dimethoxyflavone, was found to have a greater risk of causing arrhythmia, as presented in Fig. 1.

Seven phytochemical constituents were evaluated for their potential adverse effects, with Pa indicating probable activity and Pi indicating probable inactivity. Baicalein and Wogonin had a higher Pa score than Pi, showing both could cause liver toxicity. On the other hand, the 5-hydroxy-7,8-dimethoxyflavone was associated with arrhythmic action when the Pa score was greater than the Pi score. The phytoconstituents such as nor-wogonin, salvigenin, 5,7,2',3'-tetrahydroxyflavone, and dihydrooroxylin A were found to cause hepatotoxicity.

In addition, the drug-likeness of all seven phytoconstituents was evaluated, and 5-hydroxy-7,8-dimethoxyflavone obtained the maximum score, as presented in Table 2. The phytochemical constituents were also assessed for their blood-brain barrier permeationand mitochondrial toxic effect. The ADMET study profile of the seven phytochemical constituents is illustrated in the heat map shown in Fig. 2.

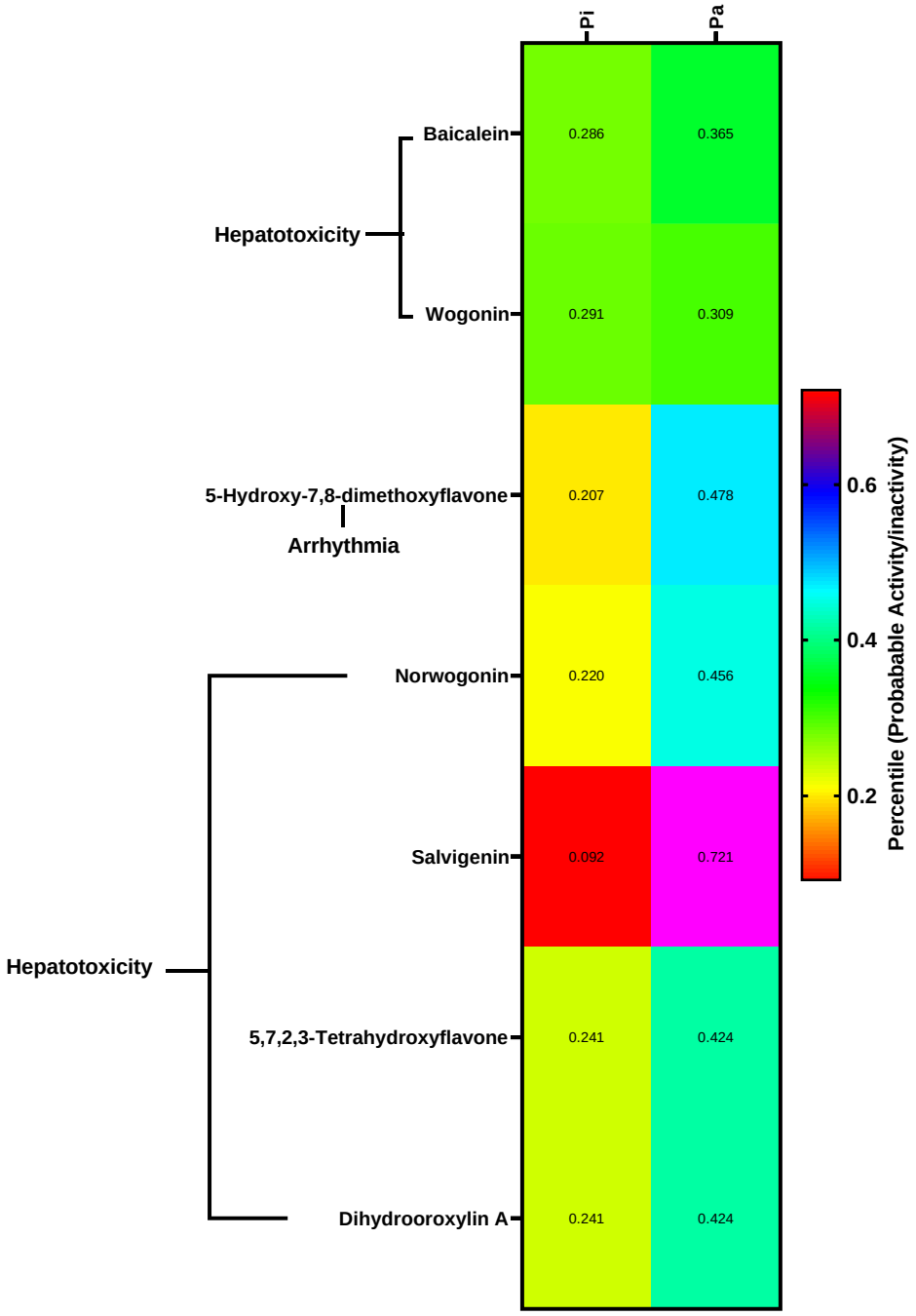

Figure 1. Toxicity prediction source: Cytoscape.

Table 2. Drug-likeness score, physical and chemical properties of seven phytochemical constituents.

Name of Phytochemical	Molecular formula	Molecular weights	Hydrogen bond acceptor	Hydrogen bond donor	MolLogP*	MolLogS*	DLS*
Baicalein	$C_{15}H_{10}O_5$	270.24	5	3	0.52	-4.74	0.10
Wogonin	$C_{16}H_{12}O5$	284.26	5	2	0.77	-4.85	0.15
5-Hydroxy-7,8-dimethoxyflavone	$C_{17}H_{14}O5$	298.29	5	1	1.01	-4.44	0.17
Norwogonin	$C_{15}H_{10}O_5$	270.24	5	3	0.52	-4.74	0.16
Salvigenin	$C_{18}H_{16}O_6$	328.3	6	1	0.70	-4.97	0.14
5,7,2',3'-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286.24	6	4	-0.03	-4.51	0.15
Dihydrooroxylin A	$C_{16}H_{14}O_5$	286.28	5	2	0.96	-4.10	0.16

*MolLogP: (octanol/water partition coefficient), MolLogS: (Water solubility), DLS: Druglikeness score

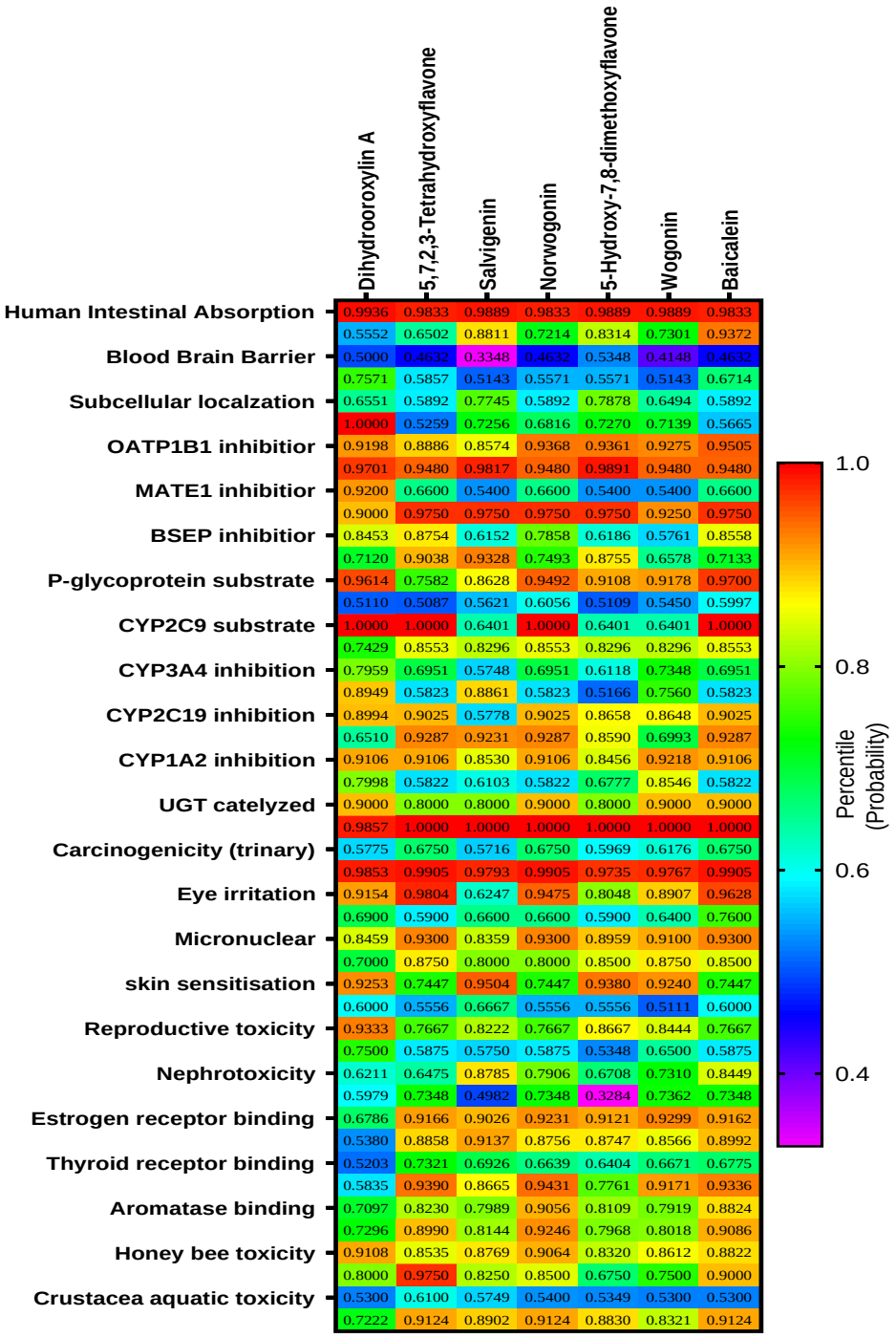

Figure 2. Screened ADMET profile of seven phytoconstituents. Within the seven phytochemical constituents, 5-hydroxy-7,8-dimethoxyflavones have the highest blood-brain barrier score of 0.5348. Its mitochondrial toxic effect was 0.325, and its acute oral toxic effect score was 0.328, clearly indicating that it had the lowest toxicity compared to the other phytoconstituents. Source: Cytoscape

3.3. Network pathway analysis.

By performing gene set enhanced examination, 10 different pathways were identified, all mediated by proteins associated with the progression of PD. Furthermore, four pathways directly associated with the modification of PD were identified by gene enrichment analysis utilizing the KEGG database index. Table 3 shows the strongest gene relationship was found in the neuroactive ligand-receptor interaction pathway.

Table 3. Pathways and proteins associated with PD are enriched in their respective gene sets.

Name of Pathway	Description	Count In Gene Set	False Discovery Rate	Genes involved
hsa04080	Neuroactive ligand-receptor interaction	6	0.0077	MAOA, ALOX5, MAOB, HTR2A, DRD4
hsa04728	Dopaminergic neuron synapse	4	0.0029	DRD4, MAOA, DRD2, MAOB
hsa05012	Parkinson's disease	4	0.0136	SNCA, DRD2, MAOB
hsa04915	Estrogen signaling pathway	3	0.0196	ESR2, OPRM1, ESR1

A network was constructed to depict the relationship between the seven phytochemical constituents, genes, and pathways. As per the network understanding, the phytochemical constituents protein-pathway has a total of 88 edges, consisting of 51 phyto chemical constituent-gene interactions and 36 gene-pathway interactions. Among the 7 phytoconstituents, 5-hydroxy-7,8-dimethoxyflavone has the greater edge count, with eleven protein counts that included HTR2A, HTR1A, SNCA, PPARG, MAOA, ALOX5, DRD4, ESR1, IGF1R, OPMR1, and SYN1. The neuroactive ligand-receptor interaction pathway modulated ALOX12, ALOX5, MAOB, and HTR2A. Notably, proteins such as ALOX5 were regulated by 5-hydroxy-7,8-dimethoxyflavones and the neuroactive ligand-receptor association pathways. Moreover, several phytoconstituents modulated these proteins, as illustrated in Fig. 3.

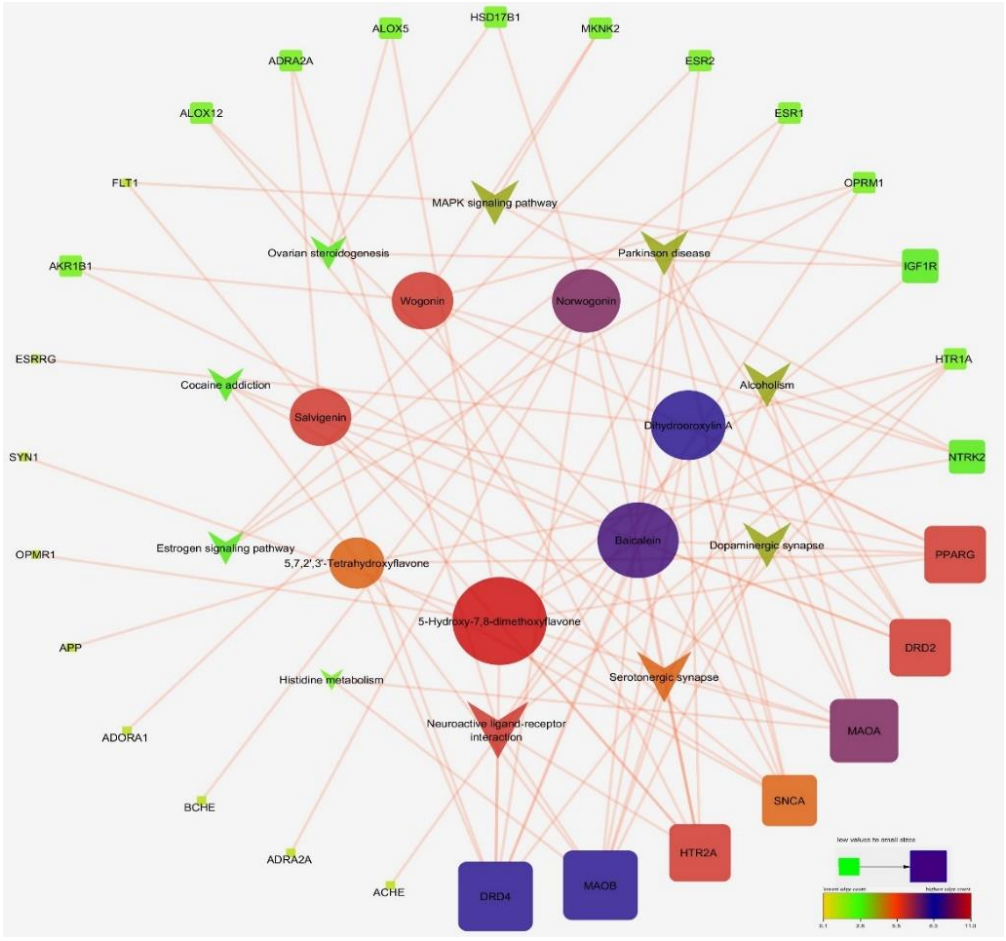

Figure 3. Network schematic representation between phytochemical constituents, protein, and pathways. Source: Cytoscape.

The network analysis showed that 5-hydroxy-7,8-dimethoxyflavone was the most modulated phytoconstituent, as it interacted with the neuroactive ligand-receptor and DRD4

gene. Both neuroactive ligand-receptor interaction and DRD4 have been demonstrated to reduce ROS and oxidative stress, resulting in neuroprotection. Phytoconstituents, genes, and metabolic pathways were linked to a network.

3.4. Gene ontology enrichment and pathways assessment.

Gene ontology enrichment and pathway analysis involve identifying cellular activities, molecular functions, and cellular components linked with a bunch of genes and mapping them onto known pathways to learn about the fundamental causes of biological mechanisms. This can better grasp cellular biology involved in disease development or other biological phenomena.

In this study, gene ontology enrichment analysis demonstrated 202 cellular activities, and further investigation identified the metabolic reaction to dopamine (GO:1903351) as the process with the minimum rate of false findings, which was modulated by 5 genes (DRD4, HTR1A, DRD2, OPRM1, HTR2A). Additionally, the analysis identified 32 molecular activities, with the lowest false detection rate being transmembrane signaling receptor activity (GO:0004888) and being modulated by eleven genes (NGFR, DRD4, HTR1A, DRD2, OPRM1, HTR2A) a total of 188 genes. Analogously, 25 biological components and 11 genes were revealed modulating a necessary component of the plasma membrane (GO:0005887) (NGFR, DRD4, FLT1, HTR1A, DRD2, OPRM1, HTR2A), as shown in Fig. 4. This information can provide valuable insights into the molecular mechanisms underlying the biological processes being studied.

The current study identified twenty KEGG pathways associated with PD. Among these pathways, hsa04080 had the lowest rate of false detection and was found to modulate 7 genes (ALOX12, HTR1A, MAOA, ALOX5, MAOB, HTR2A, DRD4). Furthermore, the networking study of the phytochemical constituent 5-hydroxy-7,8-dimethoxyflavones showed that it had greater protein regulation, with a considerable number of pathways directly found to be involved in the regulation of PD. These findings provide insights into potential targets for therapeutic interventions to manage PD.

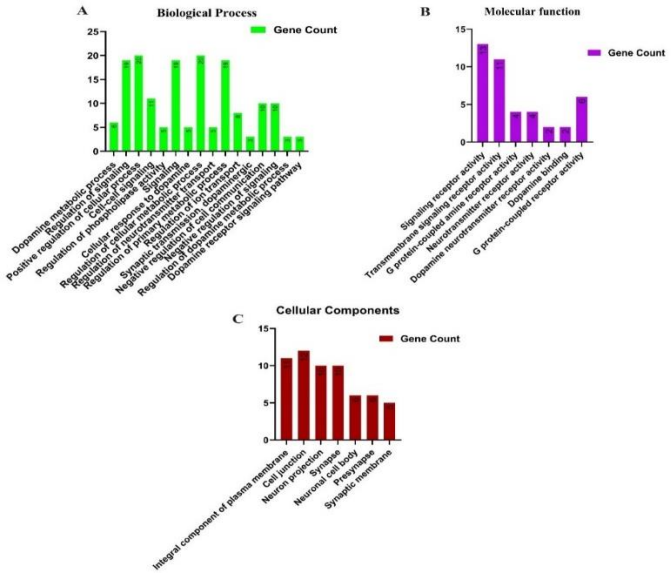

Figure 4. Gene ontology enrichment study of phytochemical constituents that modulate genes. Among the phytoconstituents, 5-hydroxy-7,8-dimethoxyflavone had the maximum degree of modulation across various targets and genes, including several pathways that have the potential to result in a neuroprotective effect. The identification of these pathways and genes can be used to guide further study on the neuroprotective effects of phytoconstituents and their potential therapeutic applications. Source: Cytoscape.

3.5. Molecular docking results.

Seven phytochemical constituents examined in this study, 5-hydroxy-7,8-dimethoxyflavones demonstrated the essential binding energy of -8.337 kcal/mol with dopaminergic receptor D4 (PDB ID: 6IQL). The interaction between the phytoconstituent and the protein was characterized by a 2-dimensional and 3-dimensional hydrogen bonding association with the Ser91 amino acid residue of the protein, as shown in Figure 5. The remaining 2-dimensional and 3-dimensional interactions between the other 6 phytochemical constituents and proteins are detailed in Table 4 and the Supplementary Files (Supplementary File-Fig.S2 and Supplementary File-Fig.S3). These findings provide information about the prospects for therapeutic applications of these phytoconstituents for treating PD. The study utilized different modules in the Schrödinger Suite 2022 to perform molecular docking simulations. The LigPrep module was used to design the ligands, and the Epik module and OPLS3 force field were employed to minimize the ligand's energy. The protein preparation module was used to prepare the protein by removing water molecules, adding missing amino acid residues, and assigning a partial charge to each atom. Finally, the Glide module was utilized to prepare the receptor grid for molecular docking simulations. These methods and tools provide a reliable and robust approach to investigating the interactions between phytoconstituents and proteins, providing insights into their potential therapeutic applications.

The Ligand Docking module was then employed to perform molecular docking simulations between the lower energy ligands in the mol format and the protein using the Extra Precision (XP) method. The docking score was examined using the Glide XP visualizer, evaluating the best docking and glide scores and the interactions with amino acid residues. These analyses identified the most favorable binding modes between the phytoconstituents and their protein targets, providing valuable information for further optimizing and developing potential therapeutic agents.

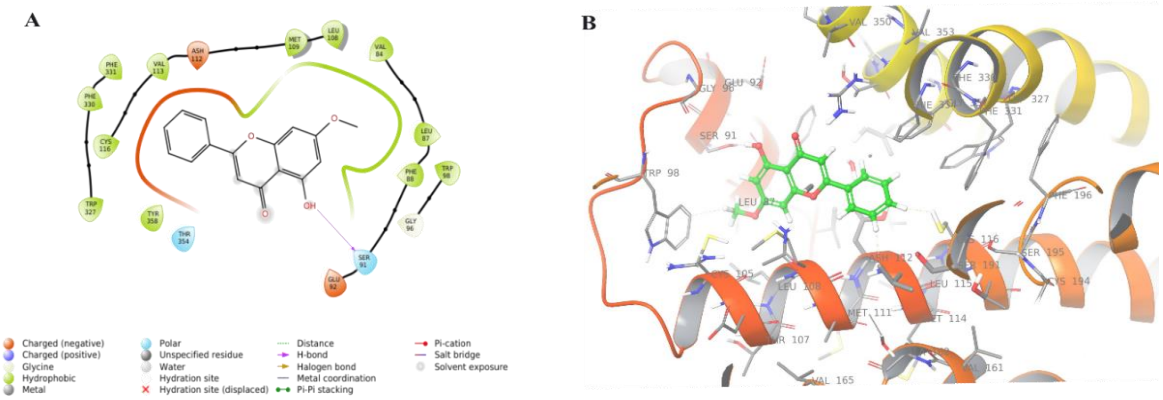

Figure 5. 5-hydroxy-7,8-dimethoxyflavone binding energy. source: Schrodinger images.

Table 4. The molecular docking outcomes of seven phytoconstituents (PDB ID: 6IQL).

Name	Binding affinity (kcal/mol)	Active amino acid residues	
		H-bond	Hydrophobic
Baicalein	-6.337	Ace182, Ser192	-
Wogonin	-7.232	Cys116, Ser191	Ser191
5-Hydroxy-7,8-dimethoxyflavones	-8.377	Ser191	Ser91
Norwogonin	-6.936	Cys116, Ser191	Ser191
Salvigenin	-6.557	-	-
5,7,2',3'-Tetrahydroxyflavone	-7.1	Ser191, Ace182	Ser191
Dihydrooroxylin A	-6.275	Ser191, Cys116	Ser191

4. Discussion

Traditional medicine has emerged as an effective therapeutic approach to treating various disorders in recent decades. Virtual methods, which include networking pharmacology, have become well-established methods for studying the therapeutic effects of natural products. Several studies have investigated the potential of *S.baicalensis*, a traditional Chinese herb, in managing PD using networking pharmacology [22]. While the important mechanism of *S. baicalensis* in treating PD remains unclear, this research aimed to build a network linking phytochemical compounds, genes, and pathways to better understand the most probable approach. The study's results identified flavonoids as potent phytochemicals that interact with proteins linked with the progression of PD. Among all the phytochemicals, 5-hydroxy-7,8-dimethoxyflavones and dimethoxyflavones demonstrated promising properties in managing PD. Further research on *S.baicalensis* has highlighted the need for these phytoconstituents to be tested in clinical trials [23,24]. It is important to highlight that 5-hydroxy-7,8-dimethoxyflavone exhibited promising interactions with other genes, indicating its potential as a therapeutic agent in slowing the progression of PD and promoting neuroprotection. Among the highly regulated genes, dopamine receptor D4 (DRD4), which plays a crucial role in activating dopaminergic neurons responsible for suppressing the progression of PD, was identified [25-27]. It is possible that 5-hydroxy-7,8-dimethoxyflavone may initiate the dopaminergic system, contributing to the biosynthesis of dopamine[28]. Altering the levels of proteins such as sirtuin 3, alpha-synuclein, and peroxisome proliferator-activated receptors may also stimulate mitochondrial biogenesis. Having their expression reduced may cause ROS to be produced, which may cause dopaminergic neurodegeneration [29]. Thus, 5-hydroxy-7,8-dimethoxyflavone may be a potent therapeutic agent for PD through its modulation of various proteins and pathways, including the dopaminergic system. Previous studies have reported the potential of *S. baicalensis* to reduce oxidative stress in manyPD animal models [27,30]. Also, four highly regulated pathways were found by doing a gene enrichment analysis using KEGG[31]. On the other hand, the dopaminergic synapse pathway (hsa:04728) directly modulates PD. It is associated with critical motor symptoms of PD, such as movement abnormalities, due to its potential to project dopamine [32]. Previous studies have shown that *S. baicalensis* has the potential to decrease apoptosis in dopamine neurons *in vitro* and *in vivo* PD models, as well as reduce various PD-induced effects in SH-SY5Y cells [33]. Dopaminergic receptor D4 (DRD4) has been found to be a general target between 5-hydroxy-7,8-dimethoxyflavone and the neuroactive ligand-receptor interaction pathway, and both are involved in cell apoptosis through inflammation. DRD4 is also associated with the excitation of neuregulin 1, a coactivator of the development of cells that promotes neuron growth and survival [34,35]. Neuronal inflammation and ROS are known to contribute to the development of cell apoptosis through cytokines. Furthermore, several studies have reported that mitochondrial dysfunctioning can enhance neuroinflammation, leading to PD [36]. Functional receptors like dopamine receptors are often engaged in signaling pathways and are associated with pro-inflammatory actions, and this pathway's most abundantly discovered regulatory site was DRD4 [37]. Dopamine neurons may be protected and supported in their function through the neuroactive ligand-receptor interaction pathway, activated by the interaction of 5-hydroxy-7,8-dimethoxyflavones with DRD4. According to the results of this research, 5-hydroxy-7,8-dimethoxyflavone is the most common flavone out of the 52 active phytochemical ingredients

that interacted with the highest number of genes related to PD. Moreover, additional study is necessary to transform these promising findings into compelling research.

5. Conclusions

When dopamine levels decrease, it can lead to a range of motor and non-motor complications, along with PD, which is mainly caused by neuronal death due to an accumulation of ROS in the brain. Researchers have discovered that phenyl-based derivatives like resveratrol may efficiently activate sirtuin 3, a protein critical in mitochondrial biogenesis. The malfunctioning of mitochondria and the resulting creation of ROS may lead to neurodegeneration. Dopamine deficiency is considered the major reason for PD. ROS, oxidative stress, and low antioxidant levels play a role in the course of PD. Further investigation is essential for a complete understanding of the complex mechanisms involved in the development and progression of PD. According to our research, we have found that 5-hydroxy-7,8-dimethoxyflavone has a high docking score of -8.337 kcal/mol and actively interacts with amino acid SER 91, as well as a high drug-likeness score and edge count. These results suggest that the flavonoid found in *S. baicalensis* may positively protect the brains of PD animal models against neuronal loss and neurotoxicity by attenuating oxidative stress. While this finding needs to be confirmed by other *in vitro* and *in vivo* experiments, we believe that *S. baicalensis* is the potential to be used as an antiparkinsonian agent.

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Conflicts of Interest

The authors declare no conflict of interest.

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Supplementary materials

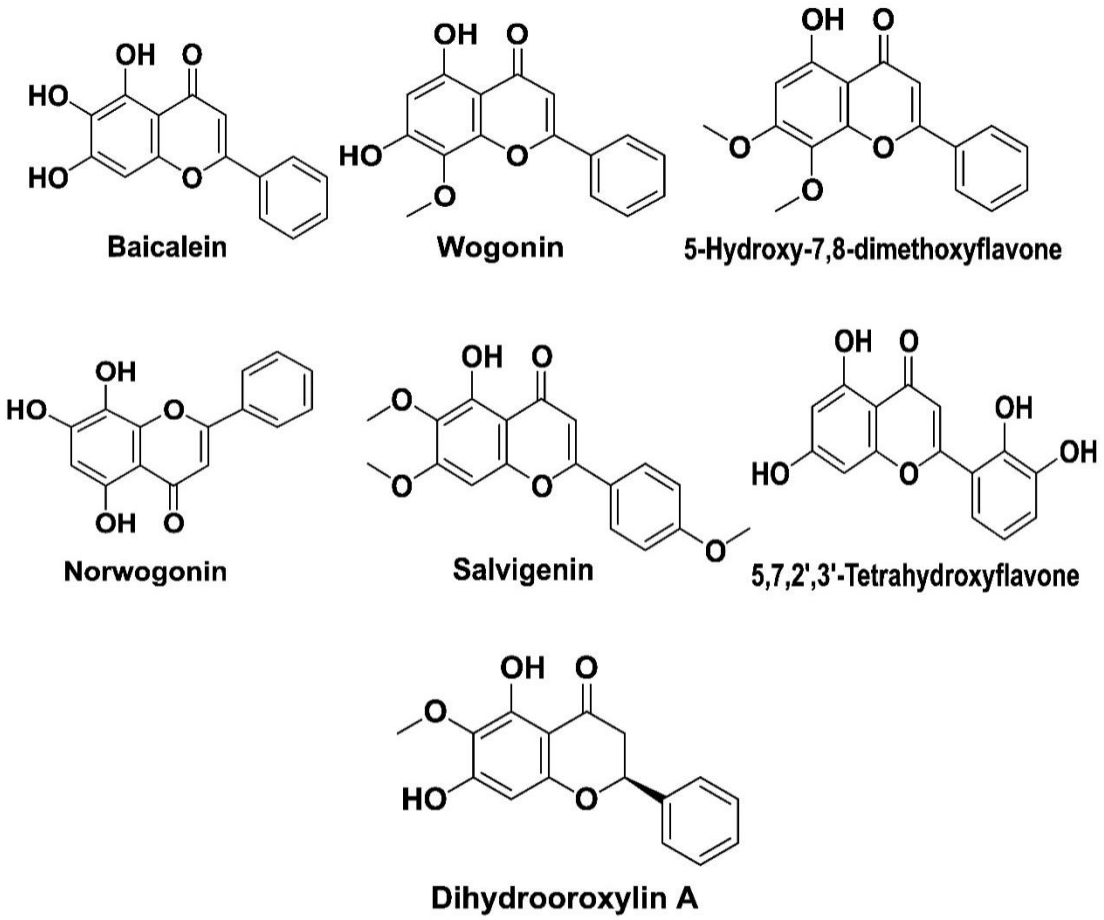

Figure S1. Structures of seven phytoconstituents from *S. baicalensis.*

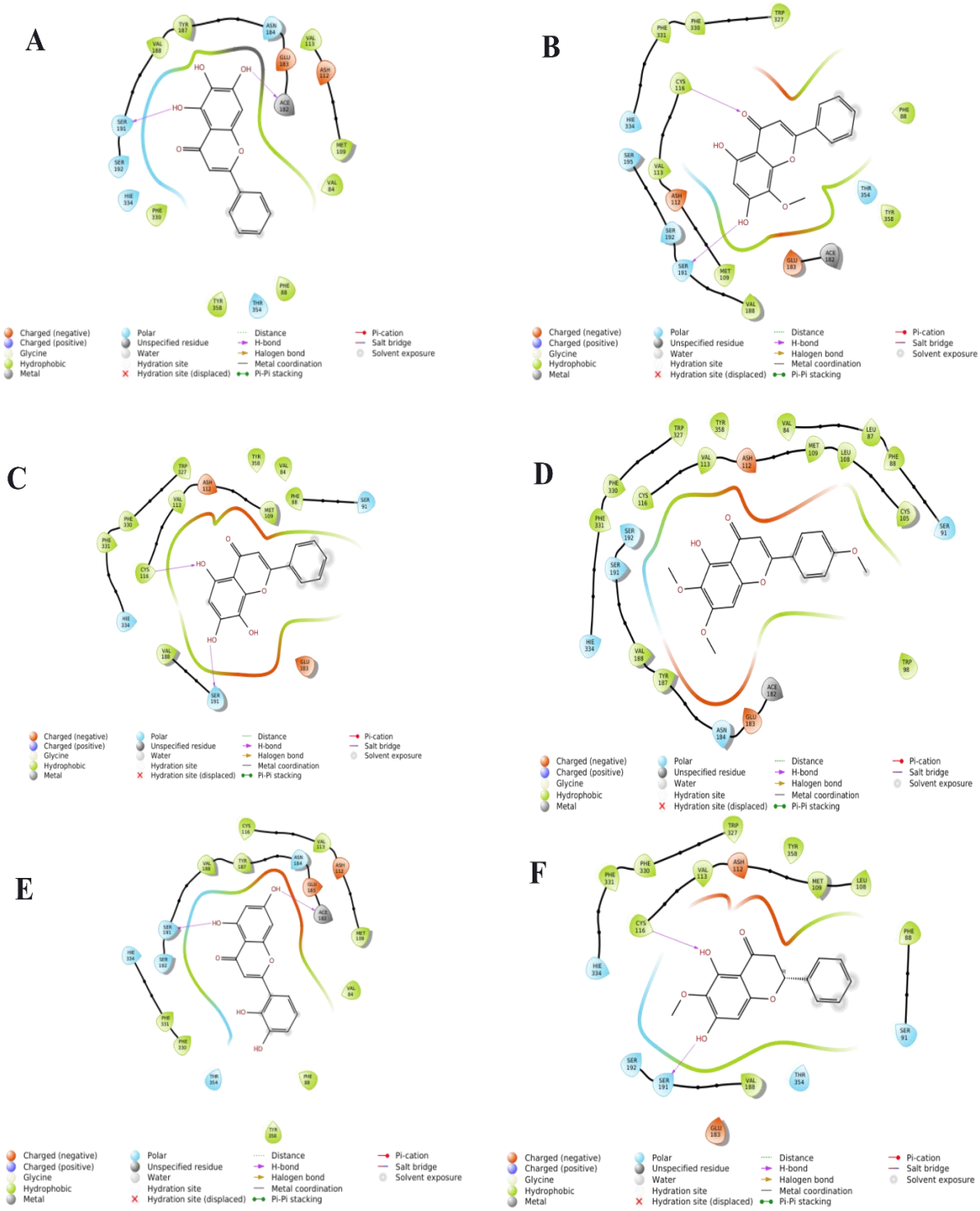

Figure S2. 2D interactions between *S. baicalensis* phytoconstituents and DRD4 Dopaminergic receptor. **A.** Baicalein **B.** Wogonin **C.** Norwogonin **D.** Salvigenin **E.** 4H-1-Benzopyran-4-one, 2-(2,3-dihydroxyphenyl)-5,7-dihydroxy- **F.** Dihydrooroxylin .

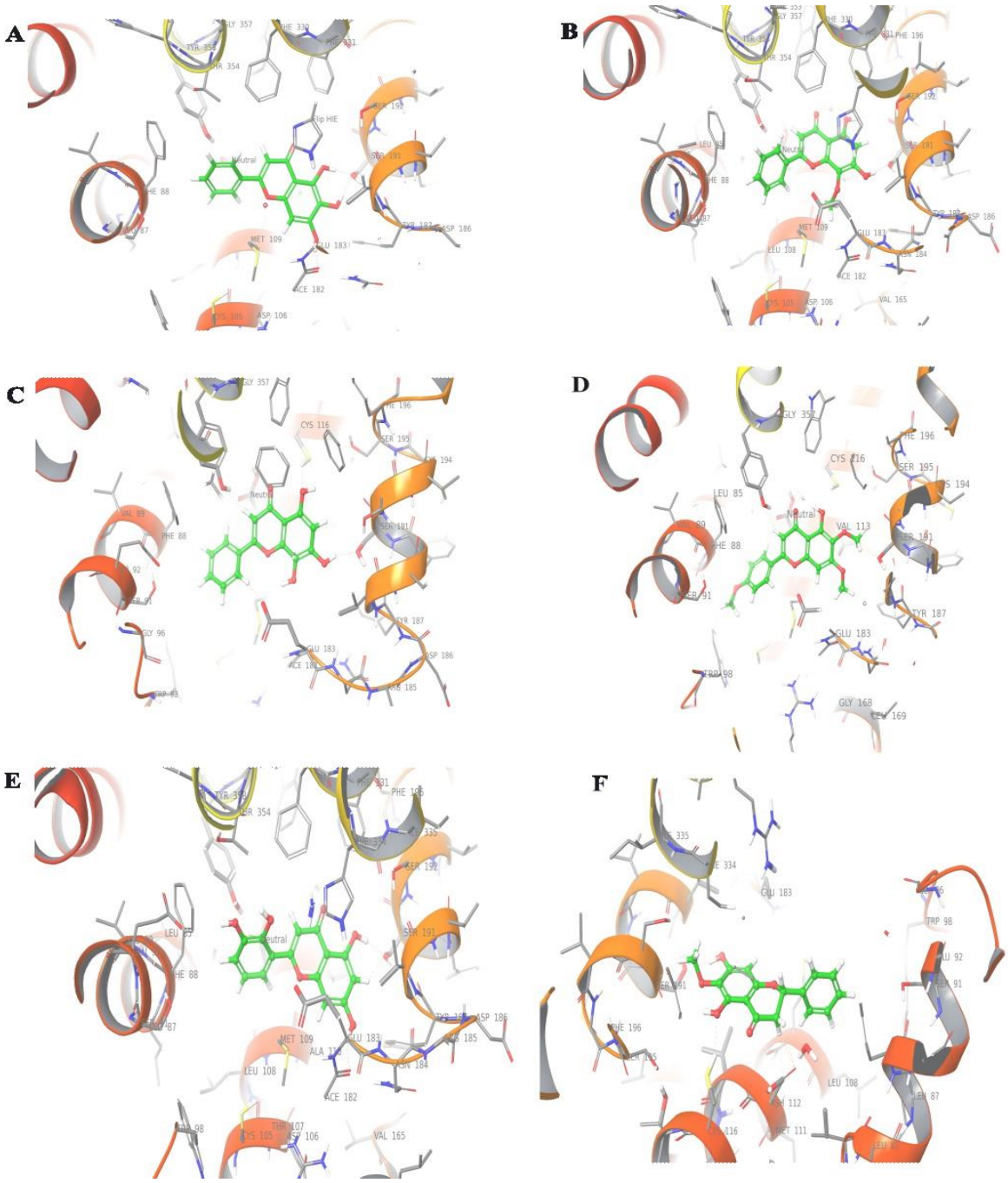

Figure S3. 3D interactions between the phytoconstituents and DRD4 Dopaminergic receptor. **A.** Baicalein **B.** Wogonin **C.** Norwogonin **D.** Salvigenin **E.** 4H-1-Benzopyran-4-one, 2-(2,3-dihydroxyphenyl)-5,7-dihydroxy- **F.** Dihydrooroxyli .

Table S1. KEGG pathways and their proteins.

ID	Description	Observed gene count	gene count	Rate of False discovery (FDR)	protein interaction (labels)
hsa04080	Interaction of Neuroactive ligand & receptor	6	330	0.007	HTR2A , ADRA2A, DRD2, HTR1A, OPRM1, DRD4,
hsa04726	Serotonergic	7	108	0.0003	ALOX12, DRD4, HTR1A, MAOA, ALOX5, MAOB, HTR2A
hsa04728	Dopaminergic	4	128	0.002	MAOA, DRD2, MAOB ,DRD4,
hsa04913	Ovarian steroidogenesis	3	50	0.003	HSD17B1 , ALOX5, IGF1R
hsa05030	addiction of Cocaine	3	49	0.003	MAOB ,MAOA, DRD2

hsa05034	Alcoholism	4	144	0.003	NTRK2, MAOB ,MAOA, DRD2
hsa00340	metabolism of Histidine	2	21	0.013	MAOB ,MAOA
hsa00360	metabolism of Phenylalanine	2	17	0.0006	MAOB ,MAOA
hsa01522	resistance of Endocrine	3	95	0.0016	ESR2, IGF1R , ESR1
hsa04066	HIF-1 pathway	3	106	0.013	IGF1R, MKNK2, FLT1
hsa05012	Parkinson disease	4	240	0.013	SNCA, DRD2, MAOB ,MAOA
hsa04010	MAPK pathway	4	288	0.015	NTRK2, MKNK2, FLT1,IGF1R,
hsa04915	Estrogen pathway	3	133	0.019	ESR2, OPRM1, ESR1
hsa05224	Breast cancer	3	145	0.023	IGF1R, ESR2, ESR1
hsa00350	Metabolism of Tyrosine	2	35	0.024	MAOB ,MAOA
hsa00260	Metabolism of Glycine, threonine and, serine	2	38	0.026	MAOB ,MAOA
hsa00380	Metabolism of Tryptophan	2	41	0.029	MAOB ,MAOA
hsa05202	In cancer Abnormal regulation of Transcriptional	3	171	0.029	PPARG , FLT1, IGF1R
hsa00330	Metabolism of proline and Arginine	2	48	0.035	MAOA ,MAOB
hsa04015	pathway **of Ras-associated protein 1**	3	202	0.041	DRD2, FLT1, IGF1R

The researchers investigated the potential genes that could be linked to the advancement of Parkinson's disease by utilizing a database (https://string-db.org/) to conduct the analysis of gene enrichment. They then analyzed the interaction of the protein network to determine the pathways and the genes associated (https://www.genome.jp/kegg/). The data was further examined to establish a possible connection between the genes, phytoconstituents, and pathways using Cytoscape 3.7.2.