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Computational analysis of phytochemicals from *Crocus sativus* L. and *Rosmarinus officinalis* L. for potential neuroprotective activity

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Neurotransmitters such as dopamine and serotonin are chemical messengers essential for normal brain function, and their imbalance has been linked to several mental and neurodegenerative disorders. The present study aims to identify natural compounds from *Crocus sativus* L. and *Rosmarinus officinalis* L. with antidepressant or anti-neurodegenerative potential for future therapeutic use, as a safer and cost-effective alternative to synthetic drugs. A series of *in silico* studies was carried out to achieve this. Phytoconstituents of *C. sativus* and *R. officinalis* were retrieved from IMPPAT 2.0 database, and descriptors were generated using PaDEL-Descriptor. Ligands with XlogP values between 1.5 and 2.7 were shortlisted and docked with dopamine D2 receptor (DRD2). The Swiss Target Prediction database was used to identify probable targets of the top compound found in the docking study. DAVID was used for gene ontology and KEGG pathway enrichment analysis. Kaempferol and DMAC-3,8 from *C. sativus* and cirsimaritin from *R. officinalis* were identified as potential agonists of the dopamine D2 receptor, as they showed strong binding with the D2 receptor comparable to a standard agonist drug. Machine learning models predicted IC_{50} values with high accuracy, while pathway analysis of the two lead compounds (kaempferol and cirsimaritin) linked them to some key neuroprotective processes, signifying their potential against depression and other neurodegenerative disorders.

Keywords: Dopamine, Gene enrichment, Neurodegeneration, Phytochemicals, *Rosmarinus officinalis* L.

Several factors, including individual lifestyle, climate change, and the COVID-19 pandemic, have contributed to the exponential rise in cases of depression and other neurodegenerative disorders worldwide in recent years[1,2]. The disease COVID continues to have a crippling effect even after the active infection has stopped because of the enduring symptoms, which include depression, anxiety, brain fog, and exhaustion. Another major factor that results in emotional as well as metabolic issues is the modern lifestyle, which includes late-night eating, artificial lighting, and erratic schedules. In the younger generation, emotional instability is exacerbated by such modern lifestyles, leading to delayed melatonin onset, an increase in nocturnal cortisol levels, interference in the serotonin and dopamine cycles, and an increase in systemic inflammation[3]. This also raises the risk of mood disorders such as depression, severely impacting a person's thoughts, feelings and actions.

The monoamine hormone dopamine is essential for behaviour, mood, attention, reward, movement, and cognition[4]. Its reduced levels, or insufficient uptake by its receptors, are considered the main causes of depression and associated disorders. Five seven-pass transmembrane G protein-coupled receptors (GPCRs) mediate dopamine's physiological effects. These receptors are divided into two subfamilies based on whether they produce or inhibit the secondary messenger cyclic adenosine monophosphate (cAMP): D1-like (D1 and D5) and D2-like (D2, D3, and D4). Research continuously shows that the D2-like receptor family has a 10–100 times greater affinity for dopamine than the D1-like receptor family[5]. Disrupted signalling of dopamine has been reported to be associated with neurological and psychiatric disorders, like depression, addiction, Parkinson's disease, and schizophrenia[6]. Thus, understanding the complexities of dopaminergic dysfunction is crucial because of its significant role in the pathophysiology of depression and other affective disorders. Continued exploration into this relationship may lead to improved treatment strategies for affected individuals.

Because of their potential therapeutic effects on neuronal function, medicinal plants are becoming an attractive substitute to the widely used conventional

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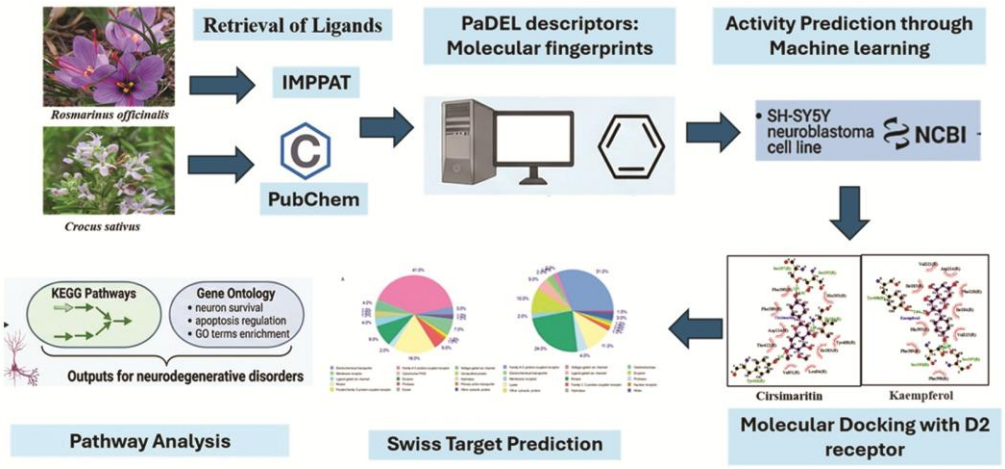

Graphical abstract

drugs. *Crocus sativus* L. (Family: Iridaceae), known as saffron in India, is widely used for its aromatic and medicinal properties. The plant has been reported to contain numerous bioactive compounds such as ursolic acid, oleanolic acid, and safranal[7]. This plant has been reported to possess neuroprotective and antipsychotic properties, with its active constituents, viz. crocins and safranal, showing beneficial effects in experimental models of schizophrenia[8,9]. A systematic review and meta-analysis of randomised clinical trials reported that saffron improves cognitive performance in patients with mild cognitive impairment and Alzheimer's disease[10]. Another medicinal plant, namely *Rosmarinus officinalis* L., or "rosemary," belonging to the Lamiaceae family is known to contain a variety of bioactive substances, including ursolic acid, rosmarinic acid, beta-amyrone and others. Various studies have reported neuroprotective and neuromodulatory properties of its active constituents capable of improving cognitive function and neuronal health[11]. Studies have reported that carnosic acid and rosmarinic acid from rosemary exhibit significant neuroprotective effects and may be beneficial in the management of neurodegenerative disorders, particularly Alzheimer's disease[12]. Based on the above studies, *C. sativus* and *R. officinalis*, were selected for the present study. The primary objective of the current study was to employ machine learning to perform an *in-silico* analysis of phytoconstituents to explore their potential for neuroprotection. For this, the active phytoconstituents of the two plants were retrieved, and subjected to molecular docking studies against the dopamine D2 receptor and the results were compared with currently available medications. Further KEGG pathway enrichment analysis was performed to identify the molecular targets and signalling pathways potentially involved in their therapeutic effects. This investigation facilitates the efficient shortlisting of possible antidepressant compounds from the large repertoire of phytochemicals in the databases, thereby conserving time, financial resources, and energy. Subsequently, these compounds can be considered for wet lab experiments and clinical trial assessment. To make the treatment more affordable, the study primarily focused on indigenous medicinal plant species native to India, which are generally safer for humans than synthetic chemical drugs.

Materials and Method

Retrieval of ligands and QSAR

The various phytoconstituents isolated from the selected plants were retrieved from IMPPAT: (Indian Medicinal Plants, Phytochemistry And Therapeutics 2.0)[13,14]. The number of ligands retrieved includes 85 and 37 from *C. sativus* and *R. officinalis*, respectively. The SDF formats of the ligands were retrieved from the PubChem database[15] and uploaded to PaDEL-Descriptor[16], an open-source software available to compute 1D, 2D, 3D and molecular fingerprints. Though, it can calculate approximately 800 descriptors, we shortlisted only 222 since we found null values under other descriptors.

Prediction of activity through machine learning

In the Machine learning technique, the training set was used to construct the model which can be applied to the test dataset for predicting their biological activity. The central focus of machine learning is taking each characteristic feature of the training set into account for prediction, and searching for the

subset characteristics that have a strong correlation with the class it is predicting[17]. For the selection of the training set, the cell line SH-SY5Y was selected for our study. It is a neuroblastoma cell line that has been used as a model for studying several neurodegenerative disorders[18]. From the NCBI database[19], we retrieved 42,667 compounds tested in this cell line, from which we shortlisted four target pathways. The calcium voltage-gated channel, cyclin-dependent kinase, histone deacetylase and tubulin pathway were the targets selected, and the tested compounds were grouped accordingly. The compounds with inconclusive and unspecified results were not considered for the study since they may interfere with the quality of the model. The SDF format of this training set ligand was downloaded, and the descriptors were generated using PaDEL-Descriptor. To reduce the noise, the descriptors with null values were excluded, and to build a good model, the best descriptors were selected. The dataset preprocessing and the validation of molecular descriptors were done using Weka[20], by selecting 'CfsSubsetEval' module with 'BestFirst' Search.

The model was constructed using a training set, and fivefold cross-validation was carried out by dividing the training set into groups, and each group was evaluated using them as training as well as a test set. Once the model was constructed, the test set was supplied, and the IC_{50} (Ki) value was calculated. Each time, the calculation was evaluated using several statistical tools and the correlation coefficient calculated for the random forest method was tabulated. This algorithm is a decision tree-based classifier, each independently built tree node is divided according to the best predictor subset that is randomly selected at each node. It has the highest accuracy in the classification of results and is known to be the best time-efficient classifier currently in use[21].

Molecular docking

The SDF format of ligands with XlogP value in the range of 1.5–2.7 (calculated using PaDEL-descriptor), were retrieved from the PubChem database. Ligands were processed using Avogadro[22] tool by adding hydrogens and optimising geometry (MMFF94) and then saved as a PDB file. The D2 receptor (PDB: 6CM4)[23] was downloaded, and removal of water and ligand was done using Pymol[24,25]. The receptor was prepared for docking by adding hydrogen and Gasteiger charges using AutoDock 4.0[26] and was subsequently saved in pdbqt format. The grid parameters include grid size of: 126 x126 x 126 with x: 156.581 y: 156.992, and z: 136.636 coordinates. After the completion of docking, a model with the lowest binding energy was saved and visualised using LigPlot 2.2.4[27].

Target prediction and KEGG pathway analysis

The "SMILES" format of ligand that recorded the lowest binding energy in the docking study for each plant was retrieved from the NCBI website and utilised for target prediction using the Swiss Target Prediction database[28]. The identified gene targets were selected for the gene ontology and KEGG pathway analysis using the DAVID tool[29,30] to find out their involvement in various signalling pathways related to neurological disorders.

Results and Discussion

QSAR

The descriptors generated using PaDEL-descriptor software have several parameters such as molecular weight, hydrophobicity, number of hydrogen bond donors/acceptors, topological indices, etc., which are known to have direct correlation with the biological activity of a compound. One such parameter, XlogP, also known as partition co-efficient assist in finding out the ADMET properties of the given drug. Any drug that targets the central nervous system (CNS) is reported to have XlogP value (a measure of a compound's lipophilicity) in the range of 1.5-2.7[31,32]. This level of lipophilicity allows a drug to effectively cross the blood-brain barrier and reach its intended target in the brain. In our study, 17 compounds of *C. sativus* and 12 compounds of *R. officinalis* were found to have XlogP values within this reported range (Tables 1 & 2). Moreover, most of these compounds did not have any Lipinski's rule violations, making them a promising candidate for further exploration as a potential drug molecule. Among the drugs tested, risperidone (dopamine receptor antagonist) recorded XlogP value of 2.709 and apomorphine (dopamine receptor agonist) recorded XlogP of 3. Despite its moderate lipophilicity, apomorphine's efficient CNS penetration is attributable to its small size.

Prediction of activity through machine learning

In our study, 2502 different training sets were used to analyse the phytochemicals separately in order to determine their IC_{50} values. The WEKA statistical parameters of the random forest classifier have been provided in (Table 3). The goodness of fit is clearly

Table 1 — Shortlisted phytoconstituents of *Crocus sativus* L. based on XlogP value and its predicted IC_{50}

S. No	CID	Name	XLogP	IC_{50}
1	10461942	beta-D-gentiobiosyl crocetin	1.629	-0.661
2	15715950	4-Hydroxy-2,6,6-trimethyl-3-oxo-1,4-cyclohexadiene-1-carboxaldehyde	1.829	0.532
3	14379528	3,8-Dihydroxy-1-methylanthraquinone-2-carboxylic acid (DMAC-3,8)	1.847	0.328
4	25244294	Dicrocin	1.86	-0.615
5	8892	Hexanoic acid	1.88	1.224
6	5280863	Kaempferol	1.915	0.009
7	44259193	[(2R,3S,6S)-6-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxochromen-3-yl] oxy-3,4,5-trihydroxyoxan-2-yl]methyl (E)-3-(4-hydroxyphenyl)prop-2-enoate	1.923	0.183
8	6544	Isophorone	1.982	1.205
9	31276	Isoamyl acetate	2.099	1.246
10	2537	Camphor	2.127	1.128
11	338	Salicylic acid	2.264	1.283
12	244	Benzyl Alcohol	2.409	1.486
13	261491	Thujone	2.434	1.019
14	61041	Safranal	2.45	1.128
15	6549	Linalool	2.468	1.273
16	637566	Geraniol	2.524	1.319
17	2758	Eucalyptol	2.595	0.931

Table 2 — Shortlisted phytoconstituents of *Rosmarinus officinalis* L. based on XlogP value and its predicted IC_{50}

S. No	CID	Name	XLogP	IC_{50}
1	381152	Piperitenone	1.529	1.289
2	5281792	Rosmarinic acid	1.578	0.495
3	14529	2-(4-Methylphenyl)propan-2-ol	1.621	1.138
4	188323	Cirsimaritin	1.699	0.212
5	29025	Verbenone	1.87	1.458
6	5281929	Methyl jasmonate	2.139	0.602
7	3314	Eugenol	2.223	1.301
8	121719	Pinocarvone	2.249	1.454
9	10582	Myrtenol	2.296	1.144
10	10364	Carvacrol	2.487	1.304
11	6989	Thymol	2.487	1.252
12	7127	Methyleugenol	2.544	1.283

evident based on the correlation coefficient of the training set, cross-validation and after splitting the data set into 80:20 and the values were found to be 0.9796, 0.7599 and 0.8. The correlation coefficient obtained were 0.9946 for the chemical drug and 0.9602 and 0.9923 for *C. sativus* and *R. officinalis*, respectively as test set, clearly indicating a positive correlation (Table 3). To validate the model, XlogP was predicted, and a scatter plot was constructed. The R value for all targets, drugs, and phytoconstituents has been compared (Suppl. Fig. S1). The range of the R value clearly shows that the constructed model can be accepted for further analysis. The same model was thus used to find out the IC_{50} value (Log10), which is otherwise known as the binding affinity of the drugs with reference to this particular cell line selected. The statistical value calculated for predicting this value was also found to be satisfactory.

Table 3 — Weka statistical parameters of random forest classifier

Name	CC	MAE	RMSE	Number of instances
Training set	0.9796	0.2236	0.3065	2502
Cross-validation	0.7599	0.6112	0.8302	2502
splitting	0.8	0.5787	0.7714	500
Drug	0.9946	0.5119	1.0115	6
C. sativus	0.9602	1.1327	1.4552	96
R. officinalis	0.9923	0.3354	0.4688	36

Molecular docking

DRD2 plays a crucial role in mediating the actions of both typical and atypical antipsychotic drugs. Both agonists and antagonists of DRD2 are employed in treating and managing diverse neurological pathologies. Agonists such as pramipexole and quinagolide are used in conditions such as Parkinson's disease, restless legs syndrome, and hyperprolactinemia, while antagonists such as risperidone, as well as partial agonists like aripiprazole, help in decreasing dopaminergic activity, thus alleviating positive symptoms of schizophrenia, such as hallucinations, delusions, *etc*.

Docking of phytoconstituents from *C. sativus* and *R. officinalis* with DRD2 showed strong interactions of some compounds with the receptor, indicating promising potential. Two compounds from *C. sativus*, namely kaempferol and DMAC-3,8, recorded binding energy of -7.51 kcal/mol and -7.1 kcal/mol, and inhibitory constant of 3.13μM and 6.25μM, respectively (Table 4). The amino acids involved in making a hydrogen bond with kaempferol were found to be Ser193, Ser197, Tyr408, out of which Ser197

Table 4 — Docking results of the top three ligands from *Crocus sativus* L. and *Rosmarinus officinalis* L., and two standard drugs with dopamine D2 receptor

Category	Name	Binding energy Kcal/mol	Ligand efficiency	KI	Hydrogen bond	Amino acid
Crocus sativus L.						
Flavonoid	Kaempferol	-7.51	-0.36	3.13uM	3	Ser193, Ser197, Tyr408
Anthracenes	3,8-Dihydroxy-1-methylanthraquinone-2-carboxylic acid (DMAC-3,8)	-7.1	-0.32	6.25uM	4	Ser197, Ser193. Thr119, Val115
Organic oxides	Safranal	-6.05	-0.55	36.84uM	1	Ser197
Rosmarinus officinalis L.						
Flavanoid	Cirsimaritin	-7.74	-0.34	2.14uM	4	Ser193, Ser197, Ile184, Tyr416
Monoterpenoid	Verbenone	-5.92	-0.54	46.04uM	1	Thr119
Monoterpenoid	Myrtenol	-5.62	-0.51	75.36uM	1	Thr372
Drugs						
	Risperidone	-10.06	-0.34	42.4nM	2	Thr119, Ser197
	Apomorphine	-8.28	-0.41	854.34nM	2	Ser193, Ser197

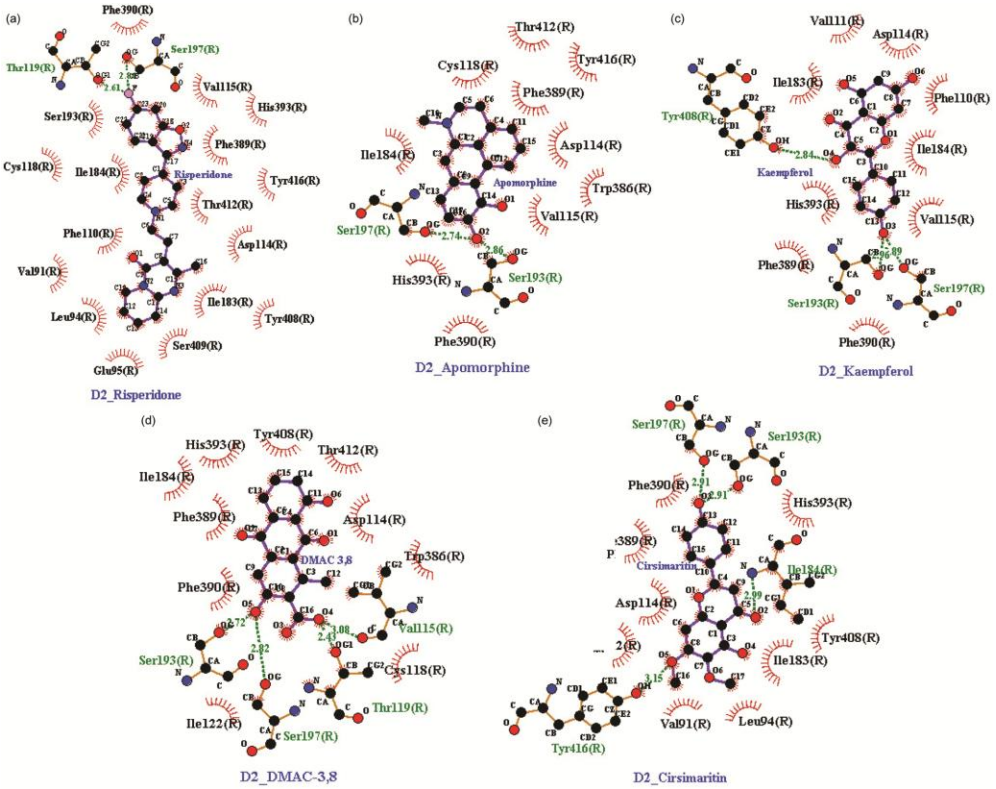

Fig. 1 — Docking pose of (a) Risperidone; (b) Apomorphine; (c) Kaempferol; (d) DMAC-3,8; and (e) Cirsimaritin with dopamine D2 receptor, showing hydrogen bond (green lines) and hydrophobic interactions (red spiked arch)

and Ser193 belong to TM5 (Transmembrane5) and Tyr408 belongs to TM7 of the DRD2. Residues Ser197, Ser193 belonging to TM5 and Thr119, Val115 belonging to TM3 of DRD2 made a hydrogen bond with DMAC-3,8 (Fig 1, and Table 4). Among the 15 *R. officinalis* compounds selected for docking, cirsimaritin exhibited the lowest binding energy of -7.74 kcal/mol with a KI value of 2.14 μM, followed by verbenone with a binding energy of -5.92 kcal/mol and a KI value of 46.04 μM. Cirsimaritin formed four hydrogen bonds, with Ser193, Ser197, and Ile184 belonging to TM5 and Tyr416 belonging to TM7 of the dopamine D2 receptor. Verbenone made one hydrogen bond (Thr119) with DRD2 that falls in the TM6 region

(Fig 1, and Table 4). Various studies on the dopamine D2 receptor have demonstrated that for an effective agonist binding strong coupling to Asp114 in TM3 and both Ser in TM5 (Ser193 and Ser197) is required[33,34]. In the present study, kaempferol and DMAC-3,8 from *C. sativus* and cirsimaritin from *R. officinalis,* all formed hydrogen bonds with Ser193 and Ser197 residues and hydrophobic interactions with Asp114 residue (Fig. 1), suggesting their probable role as a dopamine D2 receptor agonist. Two standard antipsychotic drugs, *viz*. risperidone (an antagonist) and apomorphine (an agonist), were also docked with the D2 receptor, and their binding energies were compared with that of the phytoconstituents. Risperidone (-10.06 kcal/mol) and apomorphine (-8.28 kcal/mol) recorded binding energies lower than the phytoconstituents (Table 4). Apomorphine formed hydrogen bonds with both Ser197 and Ser193, whereas risperidone formed a hydrogen bond with Ser197 but not with Ser193 (Fig 1, and Table 4). Both of them formed number of hydrophobic interactions which includes Asp114, a key residue interaction required by both antagonists and agonists (Fig. 1). The docking result is in accordance with the report by Kalani *et al*., 2004[34] that antagonists of dopamine D2 receptor make a tight contact to Asp-114 in TM3, but they do not make strong contacts with both Ser residues (Ser197 and Ser193) in TM5. A strong coupling between helices TM3 and TM5 is essential for dopaminergic transduction; and lack of this interaction in the case of antagonists leads to a weakening of the coupling, thereby inhibiting the receptor. The IC_{50} values of kaempferol, cirsimaritin and DMAC-3,8, computed using WEKA, were 0.009, 0.212, and 0.328, respectively, placing them among the top five ligands with the lowest IC_{50} values (Tables 1 & 2).

Target prediction and KEGG pathway analysis

Kaempferol from *C. sativus* and cirsimaritin from *R. officinalis* were further used. Out of 50 targets predicted for kaempferol, 24% belong to the category of enzymes, followed by Kinase (20%), Lyase, Oxidoreductase and Family AG protein-coupled receptor (8%). Target prediction for cirsimaritin revealed that 20% of the predicted targets were kinases, followed by the family of AG protein-coupled receptors at 10%. Proteases, oxidoreductases, and lyases each accounted for 8% of the predicted targets. Similar analysis for standard drug revealed that the majority of the targets belonged to the category of Family AG protein-coupled receptor, which is promising for further analysis of kaempferol and cirsimaritin as neuroprotective compound (Suppl. Fig. S2).

Based on the gene expression analysis, the top three significantly enriched cellular components for the predicted targets of both compounds were cytosol, plasma membrane, and cytoplasm (Fig. 2). This indicates that their targets are frequently found in similar cellular locations. Signal transduction was a common and highly enriched biological process for both kaempferol and cirsimaritin. While kaempferol's targets were involved in protein phosphorylation and negative regulation of apoptotic processes, cirsimaritin's targets were notably involved in transcription regulation, cell population proliferation, and chromatin remodelling.

Both compounds' targets showed strong enrichment in protein binding and ATP binding molecular functions (Fig. 3). Kaempferol's targets were also involved in identical protein binding, whereas cirsimaritin's targets were involved in zinc binding. Both kaempferol and cirsimaritin showed enrichment in metabolic pathways and cancer-related pathways. Crucially, both also affect the PI3K-Akt pathway. Cirsimaritin specifically showed significant enrichment in Alzheimer's disease pathways, which is supported by its therapeutic role in Alzheimer's disease treatment. Kaempferol, on the other hand, also showed enrichment in ROS and nitrogen metabolism pathways.

This analysis helped us to understand the mechanisms by which these compounds could work through signal transduction and interfere with several kinase activities in the pathways related to neuroactive ligand interaction and neurodegeneration pathways. Kaempferol is present in the petals in glycosylated form and reaches a concentration of up to 126 mg/g dry weight [35] which is the highest among all the other plants and spices. It has been found to have antioxidant, anti-inflammatory and anti-apoptotic properties through which it is responsible for exhibiting neuroprotective effects in several rodent models. It enhances neuronal survival; mitochondrial calcium channel activity thereby promotes neurogenesis and cognitive function[36]. The involvement of kaempferol in autophagy to mediate lipid degradation, through which its role in preventing neuronal death has been reported in a mouse model with LPS-induced Parkinson’s disease[37,38]. It has been reported to modulate several signalling pathways such as NF-kB, p38MAPK, AKT and Beta-catenin cascade, thereby reducing inflammation, which leads to age-related disorders such as Parkinson’s disease[39].

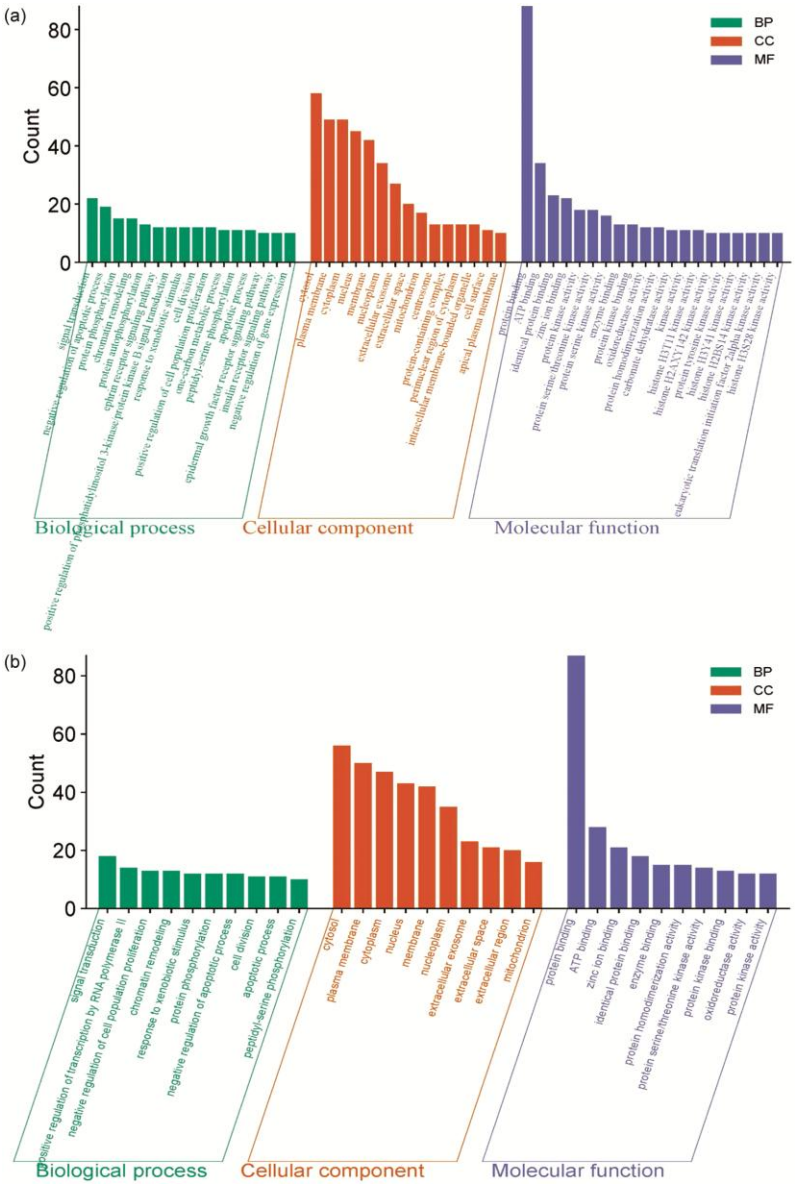

Fig. 2 — Gene expression analysis for (a) Kaempferol; and (b) Cirsimaritin

Recently, the role of this flavonoid in enhancing dopamine production and its neuroprotective role to prevent several neurodegenerative diseases has been reviewed by[40,41]. It also exhibited dose-dependent antioxidant activity in the transgenic *Drosophila* model of PD[42]. Another interesting finding is that it can protect against the motor impairment produced by pesticides in *Drosophila*.

Disruptions of metabolic pathways such as the TCA cycle, electron transport chain, and fatty acid oxidation, *etc*., have been involved in neuronal dysfunction in various neurodegenerative diseases, including Alzheimer's disease (AD)[43] and Parkinson's disease (PD)[44]. A strong correlation has been reported between the degree of clinical dysfunction in Alzheimer's disease and the magnitude of cerebral metabolic decline[45]. By positively influencing these important biological processes, cirsimaritin may protect the brain and support cognitive health.

Its enrichment in the Alzheimer's disease pathway further supports the above theory. A recent study by Zhao *et al.*[46] also reported the therapeutic role of several active compounds from *Rosmarinus officinalis* L., including cirsimaritin, in the treatment of Alzheimer's disease. These compounds were found to regulate PI3K-Akt, mTOR, and apoptosis pathways linked to neuroprotection. Experimental validation confirmed reduced neuronal cell death and inflammation.

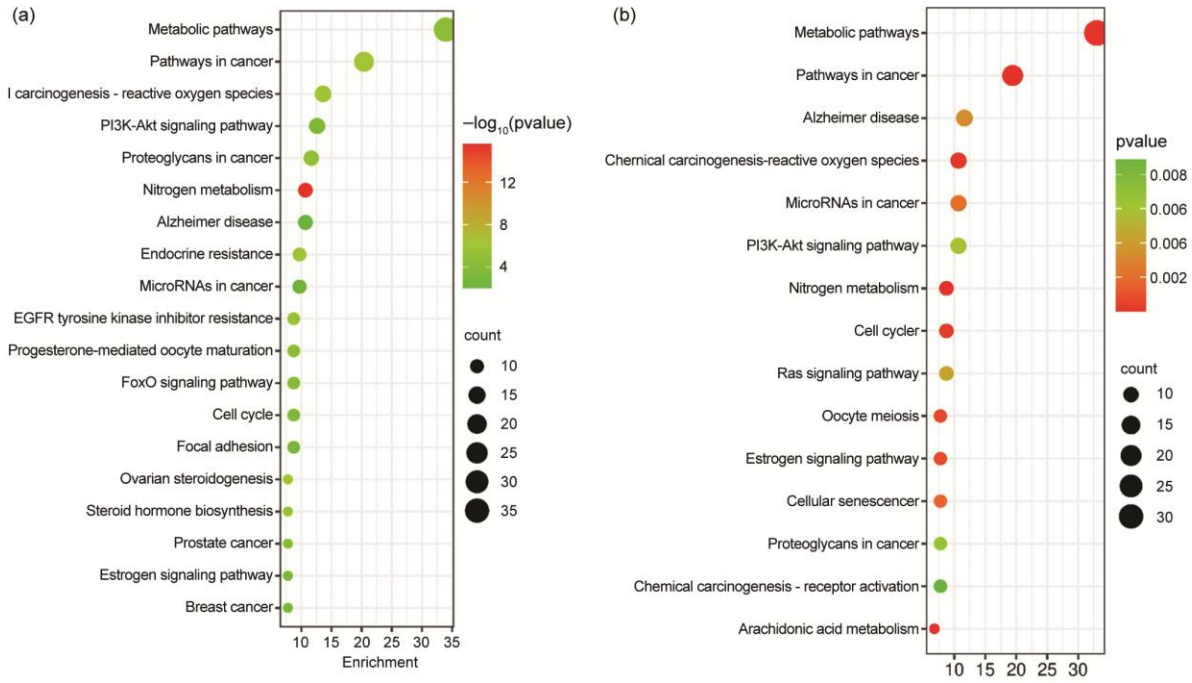

Fig. 3 — KEGG pathway analysis for (a) Kaempferol; and (b) Cirsimaritin. The size of each bubble indicates the number of significantly enriched related targets within the pathway, while the colour gradient represents the range of p-values

Moreover, research indicates that the stigma surrounding mental health issues can be diminished through educational initiatives that highlight the benefits of such natural treatments, potentially increasing their uptake among populations that historically have been reluctant to seek help. By fostering an environment where traditional remedies are validated alongside contemporary scientific approaches, we can create a holistic framework for mental health care that not only addresses the symptoms of depression but also promotes overall well-being and resilience within communities.

Conclusion

This study successfully integrated QSAR modelling, machine learning, molecular docking, and pathway analysis to identify potential neuroprotective phytoconstituents from indigenous medicinal plants, *C. sativus* and *R. officinalis*. From an initial pool of bioactive compounds, kaempferol, DMAC-3,8 and cirsimaritin emerged as lead candidates with favourable ADMET profiles with no Lipinski's rule violations, and binding affinities comparable to standard psychotropic drugs. Machine learning models demonstrated high predictive accuracy for IC_{50} values, validating the robustness of the computational approach. Molecular docking revealed strong and stable interactions of these compounds with the D2 dopamine receptor, while target prediction and KEGG pathway analysis linked their activity to critical neuroprotective processes, including signal transduction, kinase regulation, and modulation of apoptosis and oxidative stress. By emphasizing the efficacy of plant-derived compounds validated through modern computational techniques, this research bridges traditional medicine with contemporary drug discovery, paving the way for cost-effective, culturally acceptable, and scientifically sound interventions for mental health and neurodegeneration.

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Conflict of interest

All authors declare no conflict of interest.

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