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## Research Article

# Computer Simulation and Molecular Docking Studies of Natural Compounds chrysin, Morin and Luteolin for Neuroprotective Activity

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### ABSTRACT

Computer simulation studies are one of the essential stage in the novel drug development process. Insilico molecular docking studies are proved to be the best tool used to investigate the complementarity and level of interaction at the molecular level between the compound of natural or synthetic origin and a potential target. Chrysin, Morin and Luteolin are naturally occurring flavonoid compounds. These are polyphenolic compounds found as integral components of the human diet and widely distributed in plants, unicellular organisms, algae, bacteria, invertebrates, and vertebrates. These compounds possess anti-inflammatory, anti-oxidant and neuroprotective actions. In research fields, these natural compounds have been investigated as novel therapeutical agents against neurological diseases with inflammatory components, including dementia, Alzheimer disease, Parkinson disease, multiple sclerosis, stroke, and brain ischemia/reperfusion. In this study, the compounds are subjected to docking studies using Autodock vinaPyRx software.

### INTRODUCTION

Inflammation may be defined as the innate response to harmful stimuli such as pathogens, injury, and metabolic stress. The ultimate role of inflammatory process involves the restoration of the physiological homeostatic state. A Combination of genetic, epigenetic, and environmental factors involve in the pathogenesis of many inflammation-related clinical conditions (1). Primary neuroinflammatory disorders of the central nervous system that include multiple

sclerosis, neuromyelitisoptica (NMO), transverse myelitis, optic neuritis, acute disseminated encephalomyelitis (ADEM), primary angiitis of the central nervous system, autoimmune limbic encephalitis, and Susac's syndrome and multisystem diseases with inflammatory involvement of the central nervous system that include sarcoidosis, systemic lupus erythematosus (SLE), giant cell arteritis, Behçet's disease, Sjögren's, and other vasculitides (2).

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Drugs like corticosteroids,  $\beta$  interferon, Glatiramer acetate, natalizumab, plasmapheresis, mitoxantrone, B cell antagonists such as rituximab, T cell antagonists such as cellcept, daclizumab, other chemotherapeutic drugs such as cyclophosphamide and Intravenous immunoglobulin are the immunomodulatory drugs used in the CNS inflammatory diseases (6). Patients on these therapies report a risk for developing CNS opportunistic infections. Important examples of naturally derived plant compounds of neuroprotective activity included in the category of flavonoids, the secondary metabolites of various plants like tea, berries, redwine, apples and legumes. Various flavonoid compounds like quercetin, catechins, kaempferol and anthocyanidins and shows neuroprotective activity (7). Flavonoids have two phenyl ring and a heterocyclic ring, which may be responsible for the neuroprotective activity. Luteolin, Morin and chrysin are endogenous indoleamines among the flavonoids which might possess remarkable neuroprotective activity (1,2).

Various methods were developed for the assessment of neuroprotective efficacy of drugs. Among these methods, insilico computer simulation studies and molecular docking studies are widely used in the drug designing and developing processes (3,4,5). The study is done using selected macromolecule that involved in the neuronal pathways. In this study various aspects of neuroprotective activity of Chrysin, Morin and luteolin were assessed.

## **MATERIALS AND METHODS**

Insilico and Molecular docking studies of Luteolin, Morin and Chrysin of selected macromolecule were performed using various computer softwares, Molinspirationchemiinformatics and finally AutoDockvinaPyRx (3,5).

### **Molecular docking studies**

Docking software: AutoDockvinaPyRx.

Autodockvina is an open source program that developed from Molecular Graphics Lab for doing molecular docking. It achieves significant improvements in the average accuracy of the binding mode predictions compared to other docking softwares.

### **Ligand preparation:**

The chemical structure of the compounds were obtained from Pubchem express, world's largest freely accessible chemistry database. The chemical structures of the compounds were downloaded in the 3D conformer format and then converted to sdfmol format. Finally the input format prepared as pdb ligand format.

The drug likeness properties, ADME analysis and evaluation of lipinski's rule of five were done for the compounds using different online softwares like Molinspirationchemiinformatics, Pass software and Swiss ADMET softwares.

### **Protein preparation**

The macromolecule taken is the crystal structure of the "human archidonatelipoxygenase", Protein Data Bank (PDB) ID – 3D3L with resolution 2.6 Å. The protein processing was done by removing water molecules and chemistry of the macromolecule was corrected for missing hydrogen by softwares. The crystal structure of macromolecule was downloaded from the Protein Data Bank and then after processing it was converted to the input format that is pdbmol format.

## **RESULTS AND DISCUSSION**

Molecular docking continues to hold great role in the field of computer based drug design. Using insilico and molecular docking studies large number of novel ligands for suitable receptors is developed and their binding energy was calculated using the docking score. There are number of reports citing the successful application of



computer simulation methods in the drug developing program in various therapeutic areas.

The structures of Chrysin, Morin, and Luteolin that are drawn using ACD chemsketch are given in fig. 1. All molecules pass Lipinski's rule of five and their molecular description features are tabulated in table 1.

The biological activity predictor PASS server works on immediate computation of several type of biological activities on the basis of the structure of the chemical compounds. The PASS values of the compounds for different neuroprotective activities, (Antioxidant, Anti-inflammatory, MAO inhibition, Free radical scavenging) are given in the table 2. From the scores, it is clear that all the compounds possess antioxidant, free radical scavenging hence the chance of the substances being the analogues of a known pharmaceutical agent is also high. Among the compounds, Morin possess high anti-inflammatory, antioxidant and free radical scavenging activities. Luteolin possess the high MAO Inhibition action. From the toxicity and drug likeness prediction studies, it was found that all the compounds donot possess any carcinogenicity and Ames toxicity. The compounds possess high drug likeness scores and are within the drug range. Morin and Luteolin are the compounds which possess high drug likeness scores. (Table 3, Figure 1)

### **Molecular docking**

The retrieved crystal structure from PDB (PDB ID: 3D3L, Human arachidonateloxygenase) has two chains, named A and B. The compounds are docked with the 3D3L receptor and the docking scores are presented in table 4. The docked results show high docking scores with the compounds chrysin and luteolin and they possess best interaction with the active site of the receptor. The docked poses of the compounds with receptor are shown in the figure 2. The docked images show all the compounds possesses large number of hydrogen bond interactions with the receptor. The

strengthof interactions between the compounds and receptor are found to be high.

Results of docking showed that the compound binds to the active site residue, which indicates that these compounds can inhibit neurological disorders.

### **CONCLUSION**

The main objective of the study was to evaluate the natural flavonoid compounds, Chrysin, Morin and luteolin for their neuroprotective activity using computer soft wares. The study evaluated whether the compounds can be taken for therapeutic purpose by studying the molecular descriptor values, ADMET analysis and biological activity scores of the molecules. The compounds appear to be safer for administration as indicated by the computational studies. Also the molecular docking is done to find the mode and strength of interaction of the compounds with the selected receptor in the neurological pathways.

The results of molinspiration, Swiss ADMET and PASS analysis show that Morin is comparatively better drug like compound than the luteolin and chrysin. The docking score of Morin with the selected macromolecule also found to be high. The supporting results from this study argue that Morin can be further travel through several structural modification processes and detailed investigations to obtain as a newer potent agent with better therapeutic effects.

Further clinical trials are required to validate the compound.

### **ACKNOWLEDGEMENTS**

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## TABLES AND FIGURES

**Table 1: Molecular descriptor values of compounds.**

Compound	MW (g/mol)	Log P	No. of H bond donors	No. of H bond acceptors
Morin	302.24	1.88	5	7
Chrysin	254.24	2.94	2	4
Luteolin	286.23	1.4	4	6

**Table 2: Biological activity score of luteolin**

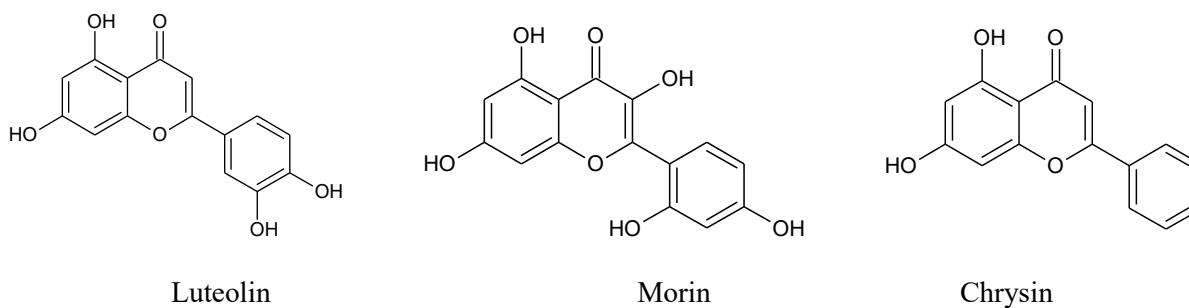
Activity	Morin	Chrysin	Luteolin
Anti-inflammatory	0.680	0.647	0.670
Antioxidant	0.858	0.717	0.782
Free-radical scavenging	0.766	0.693	0.755
MAO Inhibition	0.544	0.534	0.584

**Table 3: Drug likeness score of compounds**

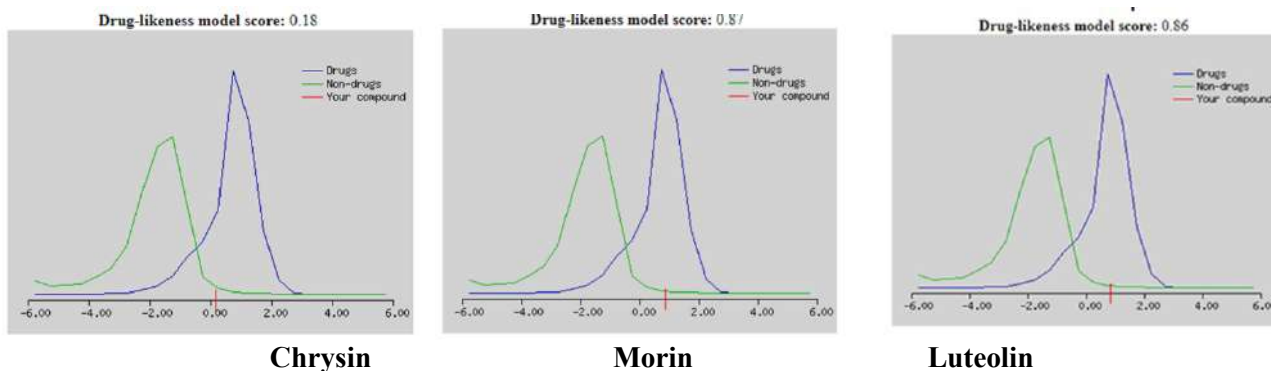
COMPOND	DRUG LIKENESS SCORE
CHRYSIN	0.18
MORIN	0.87
LUTEOLIN	0.86

**Table, 4: Docked results of compounds with 3D3L.**

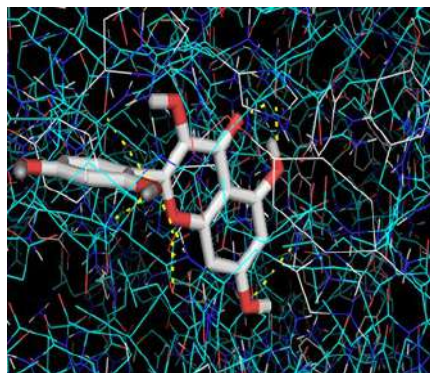
Compounds	Docking scores
Morin	-8.3
Chrysin	-9.2
Luteolin	-9.1



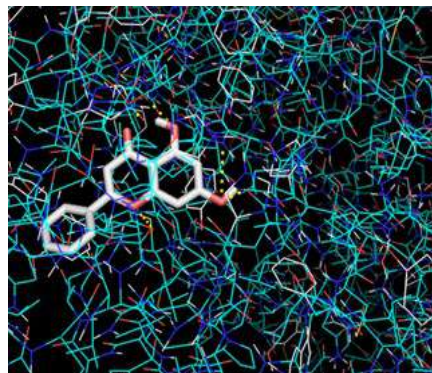
**Figure 1: Drug likeness score of compounds**



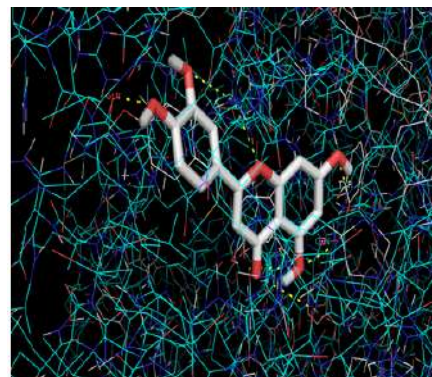
**Fig. 2: Docked images from AutodockvinaPyRx**



**Docked image of Morin**



**Docked image of Chrysin**



**Docked image of Luteolin**