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In Silico Molecular Docking of Some Selected Phytocompounds against Cathepsin S for Neuropathy

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Abstract

Aim: The aim of the present study was to perform the *In Silico* molecular docking of some selected phytocompounds against Cathepsin S for neuropathy. Chronic neuropathic pain can occur as a result of trauma or injury to a peripheral nerve. The microglial cysteine protease Cathepsin S (CatS) is critical for neuropathic pain following peripheral nerve injury. **Method:** In this study, the interaction between the phytochemical molecules Hesperidin, Urolithin A, Sinapic acid, Sulforaphane, Umbelliferone, Rutin, Naringin and the ligand binding domain of the Cathepsin S was investigated at a theoretical level by using the Mcule software, which is a program that allows docking of molecular ligands to receptor macromolecules. **Results:** The docking results show that the ligand receptor complexes are formed through hydrogen bond interactions and represented in the the form of docking score. Among of these compounds Hesperidin and Rutin shows highest docking score. **Conclusion:** This confirms the tight binding between enzyme and leads which may pave way for the discovery of new generation drugs against Cathepsin S to manage neuropathic pain.

Keywords

Cathepsin S, Docking, Neuropathic pain, Peripheral nerve injury and Phytocompounds.

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INTRODUCTION:

Neuropathic pain is one of the most debilitating chronic pain states, and more than 20 million individuals worldwide suffer from this pain. Neuropathic pain can be defined as a process occurring after a primary lesion or disease of the somatosensory nervous system [1]. The conditions and the pathophysiological states that determine the onset of neuropathic pain mostly involved are metabolic disorders (e.g. peripheral diabetic neuropathy (PDN)), neuropathies associated with viral infections (e.g. post-herpetic neuralgia, HIV, leprosy), autoimmune disorders affecting the central nervous system (e.g. multiple sclerosis and Guillain–Barre syndrome), chemotherapy-induced peripheral neuropathies, damage to the nervous system of traumatic origin (e.g. spinal cord injury (SCI) and amputation), inflammatory disorders, hereditary neuropathies, and channelopathies [2]. Drugs currently used for treating neuropathy are gabapentin, pregabalin, carbamazepine, amitriptyline, duloxetine, topical treatments (lidocaine patch, capsaicin) and opioids which are unable to alleviate the neuropathic pain [3, 4]. Adverse effects have been reported for these medicaments which limit their full clinical exploitation in the management of painful neuropathy [5]. Hence there is a need for searching

alternative therapy for the treatment of neuropathy with less adverse effects.

Currently, CatS is considered as one of the primary targets for various immune system related diseases such as rheumatoid arthritis (RA), bronchial asthma, psoriasis, atherosclerosis, myasthenia gravis (MG), multiple sclerosis (MS), chronic obstructive pulmonary diseases and also other major diseases like neuropathic pain (NP), Alzheimer's disease, cancer and obesity [6,7,8]. Cat S is a lysosomal cysteine protease predominantly expressed in dendritic cells, B lymphocytes and macrophages. Several extensive studies from the group Clark et al., [9] on inflammatory neuropathic pain revealed that the extracellular CatS released due to p38 mitogen-activated protein kinase (MAPK) pathway [10], liberates soluble Fractalkine (FKN) from neurons [9, 11] which further induced the release of inflammatory mediators that activate neurons which signals pain to the higher centers. CatS enzyme functions both intracellularly in degradation of endosomal protein bulk [10] and extracelluarly in activation and degradation of membrane proteins and connective tissue matrix respectively to implicate progressive immune disease pathways, enticing toward generation of CatS inhibitors. By using standard methods of xray crystallography, NMR as well as predictive molecular modeling methods of ligand-based and structure-based pharmacophore mapping and ligand-based 3D QSAR analysis and docking based virtual screening methods, a wide range of structural motifs have been discovered. Ligand and structure-based drug design studies of CatS inhibitors revealed their efficacy to manage the various disease condition [12].

Docking is frequently used to predict the binding orientation of drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs [13]. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand so that the free energy of the overall system is minimized. Molecular recognition plays a key role in promoting fundamental biomolecular events such as enzyme substrate, drug-protein and drug-nucleic acid interactions. Plants are rich sources of phytocompounds, and a vast majority of currently available therapeutic drugs were derived directly or indirectly from plants [14]. The aim of the current study was to identify any neuroprotective phytocompound and its possible binding efficacy with Cat S against neuropathy.

MATERIALS AND METHODS:

Selection of Target Proteins:

The X- ray crystal structure of the protein CatS (PDB ID: 3iej) with refinement of 2.180Å was downloaded from the mcule protein databank [15].

Selection of Ligands:

Some of the phytocompounds Hesperidin, Urolithin A, Sinapic acid, Sulforaphane Umbelliferone, Rutin, Naringin and Standard drug Pregabalin were selected based on their neuroprotective activity. All are having wide range of pharmacological actions and these were prepared as ligands. Pregabalin was first FDA approved drug for the treatment of neuropathy which was used as standard in our study for comparing other phytochemicals.

Ligand preparation:

The structure of the ligands (7 Phytochemicals + Pregabalin) was downloaded from Chemicalize-Chemaxon software [16]. Ligand structures were given in the mcule software. The prepared ligands were used for docking.

Molecular docking by using MCULE software:

Mcule.com is an online drug discovery platform. It offers a unique solution for pharma and biotech companies by providing the highest quality purchasable compound database and molecular modeling tools. The receptor grid was generated at the receptor site bound by a ligand. The ligands were then docked to the target proteins using mcule. The docked protein and the ligands were viewed with mcule docking score. The images of the best docked poses of the ligand and the protein were saved as .jpg files.

RESULTS:

In order to study the interaction of the compounds, we performed docking analysis by mcule software where among of these compounds Hesperidin and Rutin shows highest docking score shown in Table 1. The negative and low value of free energy of binding demonstrates a strongly favorable bond between Cat S and these compounds in most favourable conformations.

Table 1: Docking results of Phytocompounds with Cat S

S.no	Name of ligands	Target	Docking score
1	**Hesperidin**	Cathepsin S	**-9.1 -9.1 -8.7 -8.7**
2	Urolithin A	Cathepsin S	-8.0 -7.9 -7.8 -7.7
3	Sinapic acid	Cathepsin S	-6.4 -6.4 -6.2 -5.9
4	Sulforaphane	Cathepsin S	-3.7 -3.4 -3.4 -3.4
5	Umbelliferone	Cathepsin S	-6.5 -6.4 -6.3 -5.8
6	Pregabalin	Cathepsin S	-6.6 -6.4 -6.1 -5.9
7	**Rutin**	Cathepsin S	**-9.1 -9.0 -8.6 -8.2**
8	Naringin	Cathepsin S	-8.8 -7.7 -7.3 -7.2

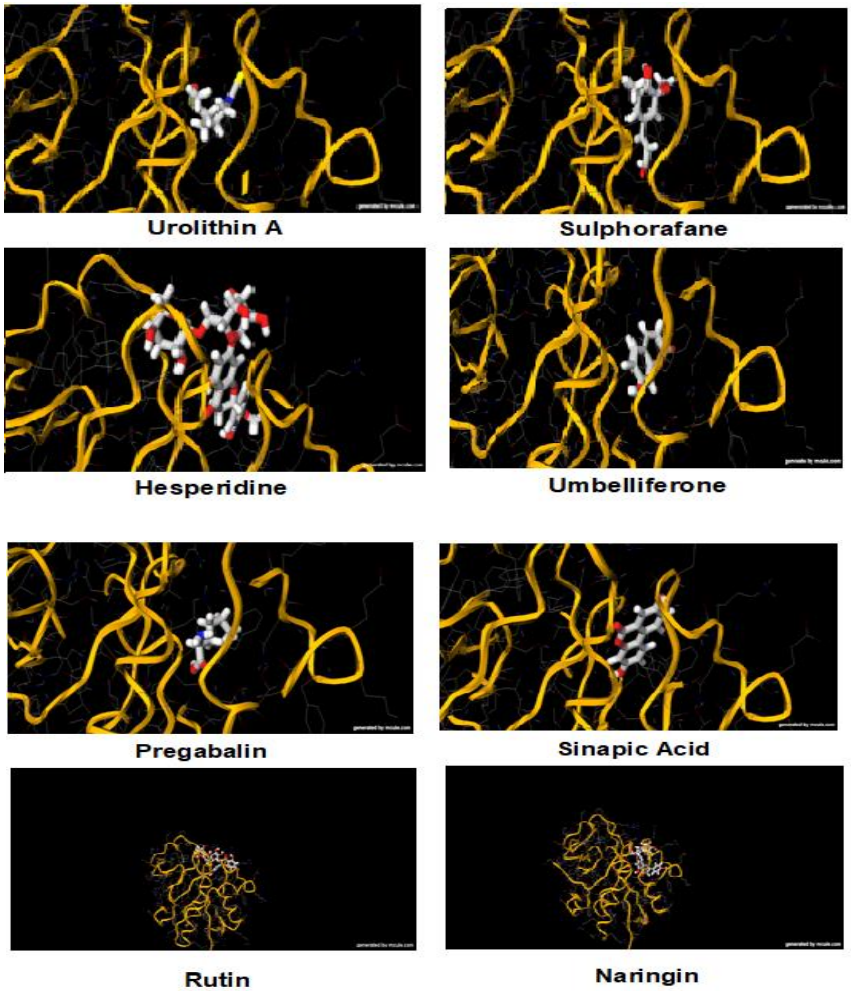

Figure 1 Best Docking Pose of the Phytocompounds

DISCUSSION:

Spinal microglia respond quickly to injury, up-regulating cell surface proteins and increasing their synthesis and release of inflammatory mediators, including cytokines and proteases that can modulate neuronal sensitivity thereby contributing to

increased nociception following nerve injury [17]. In particular, the microglial protease CatS and the neuronal chemokine FKN represent a key neuron-microglia signaling pair during neuropathic pain [9, 11, 17]. CatS is upregulated in microglial cells following nerve injury and CatS inhibitors reverse neuropathic pain behaviours [9, 18, 19]. Following microglia activation CatS is released into the extracellular environment [10], where it exerts its pro-nociceptive effects via cleavage of membrane bound FKN [9 11, 20]. Soluble FKN is then able to further amplify the pain-related enhanced response state of microglial via activation of the CX3CR1 receptor. Hence, the inhibition of microglial targets such as CatS [9, 18, 19] and CX3CR1 [21] can reduce hypersensitivity in chronic pain states. So in order to observe the ability of selected phytocompounds to bind with the CatS, we performed the molecular docking. The aim of molecular docking is the accurate prediction of the structure of a ligand within the constraints of a receptor binding site and to correctly estimate the strength of binding. The binding mode of Phytocompounds with Cat S (PDB ID: 3iej) was investigated by doing computational analysis, Mcule docking. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1. Among all the compounds Hesperidine and Rutin showed the well docking score. Because the negative and low value of free energy of binding demonstrates a strongly favorable bond is preferable for best docking study. So, the docking score between Cat S and Hesperidine, Rutin is most favorable conformations.

CONCLUSION:

In conclusion, this study sheds light on a mechanism through which these phytocompounds may have a positive effect for neuropathy.

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