International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 169-176 www.ijprajournal.com ISSN: 2456-4494

Computational docking study of Bergenin against the demyelination associated protein and their regulating receptor.

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Submitted: 01-03-2022 Accepted: 13-03-2022

ABSTRACT:
Objective: The present study was aimed to analyze the neuroprotective effect of Bergeninthrough the ADME profile assessment and molecular docking of neuronal receptors associated with multiple sclerosis. The pharmacokinetics, drug-likeness, and toxicological effect were assessed using Pre-admet. The In silico ADME (Absorption, Distribution, Metabolism, Excretion) and physicochemical properties were studied using molinspiration software. Docking studies were carried out using the Ligand fit module in Discovery Studio 4.5 an automated tool for protein molecule docking. The ADMET studies proved that Bergenin could cross the BBB and proved it as an inhibitor of CYP 3A4 substrate. The physio-chemical analysis revealed that Bergenin has an effectivemiLogP value. Docking results of Bergenin and binding affinity with proteins showed a significant binding capacity to the concerned receptors. These results conclude that the plant-based compound Bergenin may be a good physiologically favourable therapeutic medicine for neurological disease

I. INTRODUCTION

Demyelination is an impulsive disorder of the neurons which mainly affects the neurological system [1]. Multiple sclerosis has an unknown cause; however, it appears to be caused by an immune system trigger that causes demyelination and defective remyelination processes in the neurons of genetically susceptible people [2]. Auto immune-mediated disorders like multiple sclerosis involve disturbance of the blood brain barrier and their relative neuronal functions [3] which lead to the deprivation of neurotrophic factors. Moreover, neuroinflammation, astrocyte scarring, and microglial damage are all signs of demyelination, which leads to the death of oligodendrocytes and the rupturing of myelin sheaths. [4,5]. The multilaminar lipid sheath myelin is vital for the communication of neurons on the nerves and is formed by the process of myelinogenesis. Therefore, myelin insulation around neurons is essential for the effective function of the neuron signalling process.

Myelination signallingcascade involves many functional receptors and associated coreceptors proteins among this NgR1 receptor and NOGO-Aprotein play animportant part in the demyelination process in neurons [4].The CNS-specific axonal regeneration inhibitory protein is Nogo-A(Neurite outgrowth inhibitor A).It is amembrane-associated protein that has regulatory functions on evolving brain, whichincludes migration of oligodendrocyte cells, neurite formation, and growth-inhibiting action during CNS maturation.NOGO A binds to Nogo receptor1 (NgR1), a glycosylphosphatidylinositol protein that needs signalling molecules to suppress myelin effectively. The NgR1 receptor requires two alternative coreceptor complexes, such as P75 or Troy, and Lingo-1 (Leucine rich receptor) to transduce the signals associated with axonal demyelination. Activation of the NgR1 signalling complex inhibits axonal proliferation via the RhoA pathway [5,6]. Lingo-1, a co-receptor [19,20], is broadly expressed in the CNS. To generate a functional receptor for myelin inhibitors, LINGO-1 binds to both NgR1 and p75ntr. The inhibitory action of myelin proteins is diminished in the absence of LINGO-1.In addition, myelin fragments and glial damage are the key inhibitory factors in synapse formation in CNS regeneration [7], and they are regulated through NOGO receptor-interacting protein 1 and with their corresponding co-receptors p75 and leucine-rich receptor LINGO-1 and oligodendrocyte myelin glycoprotein (Omg).

Bergenin is an isocoumarin isolated from medicinal plants such as Bergenia crassifolia,

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 169-176 www.ijprajournal.com ISSN: 2456-4494

Bergenia linguata, Bergenia ciliata , Bergenia stracheyi. Ardisia elliptica and in Mallotus japonicus [8,9]. It also possesses various therapeutic properties such as hepatoprotective, antiulcer agent, neuroprotective, and immunostimulatory effects of bergenin have been discovered [10]. Thus, in silico investigations were used to explore the neuroprotective impact of Bergenin as a therapy medication for Multiple sclerosis by modulating the main inhibitory receptor protein Ngr1 and associated NOGO-A protein involved in axonal regeneration.

II. MATERIALS AND METHODS

2.1. In silico Drug-Likeness and ToxicityPredictions

Pre-Admet was used to estimate in silico pharmacokinetic parameters and other molecular characteristics using the structure of bergenin. The number of hydrogen donors, hydrogen acceptors, rotatable bonds, total polar surface area, and synthetic accessibility of the compounds were all reported by the Pre-Admet predictor. Lipinski et al. screens using the Pre-Admet predictor were also performed on the ligands. The pharmacological qualities of pharmaceuticals are determined by drug-likeness, which is a prediction. This prediction is based on the Lipinski rule of five, which was first proposed by Lipinski et al. When a chemical has more than 5 H-bond donors, 10 H-bond acceptors, a molecular weight larger than 500, and a computed LogP (CLogP) greater than 5, the rule predicts poor absorption or penetration. The selection of compounds as drug candidates were determined by a parameter called drug score. The higher the drug score value, the higher the chance of the compound is considered as a drug candidate.[11-14]

2.2. Mol-inspiration studies

ThePhysio-chemical chemi-informatics of Bergenin
was analyzed for the prediction of bioactivity and chemical properties of the drug using https://www.molinspiration.comsoftware. [15].

2.3. Preparation of Ligand

The three-dimensional structure of Bergenin an active phytochemical was retrieved from PubChem and ChemSpider database in '.sdf' and '. mol' formats. These are then used as ligands for docking against the target.

2.4. Molecular docking studies

Docking Studies Docking was carried out using the Ligand fit module in Discovery Studio 4.5 which is an automated tool for protein molecule docking/scoring. The 3-dimensional structure of Bergenin (PubChem ID: 66065), were retrieved from PubChem and optimized for docking using Discovery studio. The protein Crystallographic structures of receptors (NgR)1 (PDB ID: 5o0o), were retrieved from www.rcsb.org and,NOGO A was designed using iTasser online site for protein modelling and used for docking studies by deleting all heteroatoms, ligands, and water molecules and optimized by minimization of energy by using Discovery studio. The obtained structures were saved and used for the docking studies [16].

The Ligand fit module in Accelrys Discovery Studio 4.5, which is an automated tool for protein-small molecule docking/scoring [17], was used for docking. The procedure is as follows: For energy minimization, the CHARMm forcefield is used to the protein structure. All water molecules were removed, hydrogen atoms were added to the protein, and the ligand was stabilised using clean geometry. Identify the binding location (ligand-based or cavity-based). Dock a ligand to each receptor's binding site. Save the constructions that are moored at the top (diverse poses).

III. RESULTS

3.1. ADMET studies

The ADMET studies proved that Bergenin could cross the BBB (blood-brain barrier) (Table.1), with a permeability score of +0.131559, and proved it as an inhibitor of (Cytochrome P 450) CYP 3A4 substrate. The drug has got a good ability to absorb in the human intestine (28.268982) and has a negative skin permeability score (-4.96971). The drug likeliness analysis revealed that it is not violating Lipkin's rule of five (Table 2). The Toxicity prediction revealed that the drug has negative toxicity in most of the predicted animal models (Table 3). These properties ensure its utility as a better choice for neuroprotective action.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 169-176 www.ijprajournal.com ISSN: 2456-4494

TABLE 1: ADMET Preicions for Bergenin using Pre-ADMET

Parameters	BERGENIN
BBB	0.131559
CaCo2	18.6778
Buffer solubility mg/L	35868.1
CP2C19 Inhibition	Inhibition
CP2C9 Inhibition	Inhibition
CYP2D6 inhibition	Non
CYP2D6 substrate	Non
CYP3A4 inhibition	Inhibition
CYP3A4 substrate	Weakly
HIA	28.268982
MDCK	1.07832
Plasma protein binding	36.341321
Pure water solubility mg/L	37052
Skin permeability	-4.96971
SKlogD_value	-0.653860
SKlogP_value	-0.653560
SKlogS_buffer	-0.961530
SKlogS_pure	-0.940450

Data represents values for Blood brain barrier penetration (BBB), CYP- cytochrome P450 inhibition ,Human intestinal absorption (HIA), octanol-water partition coefficient (logP), solubility (logS).

Table 2: Durglikness values for Bergenin using Pre-Admet tool

ID	VALUE
CMC like Rule	Not qualified
CMC like Rule Violation Fields	AlpoP98_value
CMC like Rule Violations	1
Lead-like Rule Violation Fields	AlpoP98_value
Lead like Rule	Violated
Lead like Rule Violations	1
MDDR like Rule	Mid structure
MDDR like Rule Violation Fields	No_Rotatable_bond
MDDR like Rule Violations	1
Rule of Five	Suitable
Rule of Five Violation Fields	-
WDI like Rule	0
WDI like Rule Violation Fields	In 90% cut-off
WDI like Rule Violations	0

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 169-176 www.ijprajournal.com ISSN: 2456-4494

Data represents values for various druglikeness rules. MDDR- MDL Drug Data Report; CMC- Comprehensive Medicinal Chemistry; WDI- World Drug Index

Table 3: Ames test and carcinogenicity predicions for Bergenin

Parameters	Value
Ames test	Mutagen
Carcinogenicity in rat	Negative
Carcinogenicity in mouse	Negative

Data represent predicted values for Ames test and carcinogenicity for rats and mice.

3.2. Analysis of physio-chemical properties

The physio-chemical analysis revealed that bergenin has a miLogP (Molinspiration log p-value) of -0.90 and TPSA (Total polar surface area) of 135.91 stating it as a water-soluble drug with relatively better physio-chemical properties essential for a treatment drug (Table 4). Moreover, Biological activity prediction revealed that Bergenin can act as a GPCR (G-protein coupled receptors ligand,) thus providing an insight into its molecular basis of action in the cells (Table 5).

Table 4: Analysis of physio-chemical properties of Bergenin using Mole inspiration

MoleinspirationPhysio-chemico Property	Values
milogP	-0.90
TPSA	145.91
Natoms	23
Molecular weight	328.27
n0N	9
n0HNH	5
nviolations	0
nrotb	2
volume	265.89

Data represents the milogp and TPSA valuer for physicochemical properties of Bergenin

Table 5: Biological activity of Bergenin using Mole inspiration

Mole inspiration bioactivity	Score
GPCR Ligand	0.60
Ion channel modulator	-0.90
Kinase inhibitor	-0.90
Nuclear receptor ligand	-0.80
Protease inhibitor	-0.14
Enzyme inhibitor	0.35

Data represent the values for biological ligand, modulator, and inhibitor activity of Bergenin

3.3 Interaction of Bergenin with NgR1, NOGO-A and their associated co-receptors

The docking analysis revealed that Bergenin could actively inhibit and interact with NgR1and corresponding co-receptor protein with good docking score and hydrogen binding site proved that their interaction has an efficient ligand efficacy with Bergenin with amino acid interactions by forming pi-anion and Vander wals forces, conventional hydrogen, and Pi-alkyl.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 169-176 www.ijprajournal.com ISSN: 2456-4494

Fig. 1. Docking analysis showing the interaction of NOGO Receptor 1 (NgR1) with Bergenin 3D interaction between protein and Ligand. 2D ligand-protein interactions

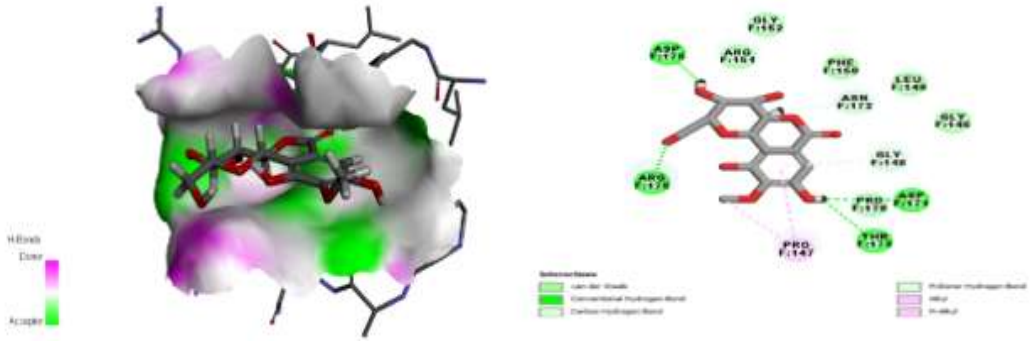
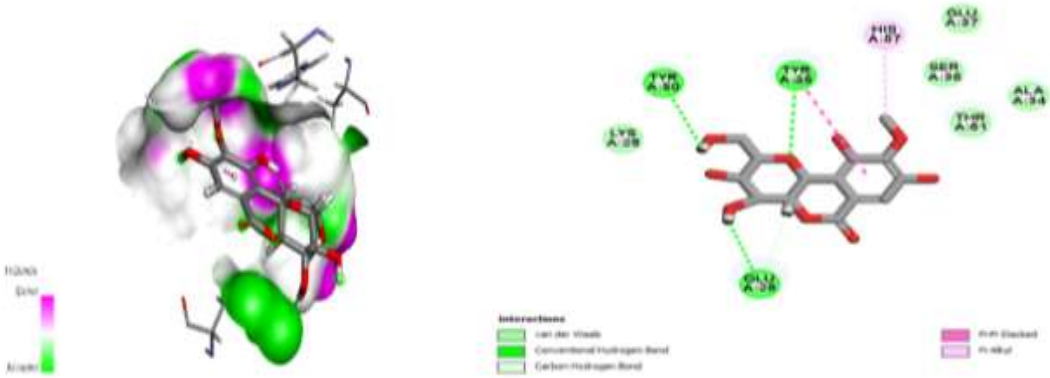


Fig. 2. Docking analysis showing the interaction of Neurite outgrowth Inhibitor (NOGO A) with Bergenin. 3D interaction between protein and Ligand. 2D ligand-protein interactions



IV. DISCUSSION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that causes significant neurodegeneration in MS patients. CNS demyelination is linked to decreased nerve conduction as well as a decrease in motor and cognitive functions [18,19]. Many neurodegenerative disorders are being treated with natural plant-derived secondary chemicals. Bergenin is a plant-derived chemical that has been shown to have neuroprotective properties. As a result, an in-silico examination of Bergenin's neuroprotective impact on MS pathology-related proteins was carried out in this work. Many physiologically active qualities have been described, including antihepatotoxic, antiulcerogenic, antiarrhythmic, neuroprotective, anti-inflammatory, and immunomodulatory capabilities. [20].

Pharmacokinetics is the study of a drug's absorption, distribution, metabolism, and excretion over time. To predict pharmaceutical partitioning between the blood and the brain, the log BB value is employed. Compounds that are lipophilic are dispersed through the blood-brain barrier (BBB). High lipophilic substances flow through the BBB due to diffusion, whereas low lipophilic molecules pass through due to specific carriers. In order to be successful, CNS therapeutic drugs must be able to penetrate the BBB. Compounds with a logBB value more than 0.3 have a high absorption to the CNS, those with a logBB value between 0.3 and 1.0 have a medium absorption to the CNS, and those with a logBB value less than -1.0 have a low absorption to the CNS.According to our data, bergenin has a moderate absorption rate in the CNS. Bergenin has a good BBB penetration as a result. Because MS is a brain disease, any treatment for MS must have a high level of BBB permeability. Human intestinal absorption is the process by which drugs are absorbed from the gut into the bloodstream (HIA). Compounds with absorption rates of 0-20 percent are poorly absorbed, those with absorption rates of 20-70 percent are moderately absorbed, and those with absorption

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 169-176 www.ijprajournal.com ISSN: 2456-4494

rates of 70-100 percent are well-absorbed. In our findings, Bergenin has substantially higher HIA values. Protein binding has an impact on a drug's effectiveness. Drugs bind to albumin and other plasma proteins.Medicines' half-lives are influenced by their interactions with plasma proteins. A medication's plasma protein binding should be minimised for diffusion and distribution across the body. Drug protein complexes are too large to pass through the plasma membrane. Bergenin binds to a very small number of plasma proteins, according to our findings. The difference in pharmaceutical binding to plasma proteins might be anything from 11 and 82 percent. The drug's efficacy is influenced by plasma protein binding over a threshold of 80-85 percent. The octanol-water partition coefficient (logP) and molecular weight are thought to have an impact on the excretion process that eliminates the molecule from the human body. The log P scale is used to determine lipophilicity. In the membrane permeability equation, it is a critical variable.The greater the lipophilicity of a chemical, the slower its metabolism and absorption. It's also more prone to bind to undesired hydrophobic macromolecules, perhaps causing toxicity. The hydrophobicity of medication increases, making it less soluble in the stomach and more soluble in fat globules. Bergenin has a lower logP value than, suggesting that it is less lipophilic and absorbs more readily. The body will try to get rid of the drugs or xenobiotics. The Cytochrome P450 enzymes are in charge of drug metabolism in the liver. The enzymes CYP3A4, CYP2D6, CYP2C9, and CYP2C19 help with drug metabolism. Each drug has a different interaction with CY450. Drugs can either inhibit or increase the cytochrome P450 enzymes.Drugs may or may not inhibit or stimulate all kinds of CYP450 enzymes. One CYP450 is adequate for metabolism. Caco-2 and Madin-Darby canine kidney (MDCK) monolayers are used to test oral absorption. They also include transporter proteins. According to our ADMET experiments, bergenin might be a good physiologically usefultreatment drug for brain-related illnesses like MS. [21,22].

4.1. Druglikeness

Drug likeness is a concept that enhances a drug's pharmacokinetics and pharmacological properties, such as solubility, chemical stability, distribution profile, and bioavailability, and may therefore assess if a molecule is similar to known treatments. It's made up of a number of molecular descriptors that all follow their own set of rules [23]. Descriptors are physicochemical or structural aspects of a molecule that are used to assess attributes such as lipophilicity, solubility, and absorption in humans. [24]. According to Lipinski's rule, if logP> 5, molecular weight > 500, number of hydrogen donor groups > 5, and number of hydrogen acceptor groups >10, a drug's absorption will be impeded. The MDDR like a rule, CMC like rule, and WDI like rule are based on molecular descriptors other than those mentioned in Lipinski's rule [25] for substances registered in the MDL Drug Data Report (MDDR) database, Comprehensive Medicinal Chemistry (CMC) database, and World Drug Index (WDI) database. Lipinski's rule, also known as the Rule of Five, the WDI like rule, and the Lead-like rule, as well as any of the other drug resemblance criteria, were qualified by Bergenin (Table 2).

4.2. Toxicity and Pharmacodynamic Studies

Toxicity studies predicted Bergenin to be a non- mutagen but non-carcinogenic in rats. (Table 3). Pharmacodynamics states the relationship between the drug concentration at the site of action and the effects-positivity or negativity- it produces in the time course

4.3. Docking studies

Molecular docking is frequently used for drug design studies. Molecular docking is optimization research that determines the "best fit" orientation of a ligand that will attach to a target protein. The chemical that binds to the protein of interest is known as a ligand [26] The Ligand Fit module in Accelrys Discovery Studio 4.2 was used to discover the probable binding location of the receptors involved in myelin formation in this investigation. A cavity detection approach is used in Discovery Studio's ligand fit docking. It generates ligand confirmations using the Monte Carlo method, which are then docked to the protein's active site [27]. In our study, Bergenin was docked to all the binding sites, and the one with the highest docking score in each molecule was chosen. Dock score is a force field-based scoring formula that is simple to use. Bergenindocked with receptor proteins and had a good docking score.

Detailed analysis of the best-docked pose of Bergenin to PDB 5o0o showed that

Grid spacing 0.5,Grid origin-10.26,71. 29,77.601, Ligand score1 deriving 5.08, Ligand score2 deriving 4.91, -PLP1 (Piecewise Linear Potential)88.23. -PLP2 85.06, -PMD-0.94, Ligand internal energy-3.308, and number of highly docked pose 10 and the amino acids involved in interaction were ASN 172(Asparagine), GLY 128(Glycine)by Pi-conventional hydrogen bond, Pi-Alky bond PRO 147 (Proline), by conventional hydrogen bond ASP (176) (Aspartate), ARG (175) (Arginine),

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Volume 7, Issue 2 Mar-Apr 2022, pp: 169-176 www.ijprajournal.com ISSN: 2456-4494

ASP(171)(Aspartate)and THR (173) (Threonine) with a docking score of 60.003.(Figure1)

Grid spacing 0.5, Grid origin 41.115,21.181,13.898, Ligand score1 deriving 2.36 Ligand score2 deriving 3.52, -PLP1 (Piecewise Linear Potential)42.4. -PLP2 40.52, -PMD-130.93, Ligand internal energy-0.94 and number of highly docked pose 10 and the amino acids involved in interaction with NOGO A were Pi-Pi stacked bond TYR35 (Tyrosine) Pi-alkyl bond with His 57, and conventional hydrogen bond with amino acids TYR 50 (Tyrosine), TYR 35 (Tyrosine), GLU 26 (Glutamate). The docking score of NOGO A with Bergenin ligand is 25.578.(Figure 2). From the docking results of the two proteins, the NgR1 shows a high docking score and NOGO A shows a potential docking score and binding affinity with Bergenin Therefore, the study concludes that Bergenin has a possible binding effect on the neuroreceptors proteins in the brain.

V. CONCLUSION

The present study showed Bergenin, a plant-based natural compound that is essential for a molecule to be classed as medication has effective pharmacokinetics and drug-likeness criteria. Bergeninhas potential blood-brain barrier penetration, increased intestinal absorption, less excretion, follows Lipinski's rule, and has an effective docking score to NgR1 and NOGO-A, according to the findings of this study. Bergenin may block negative regulatory receptor proteins involved in axonal regeneration in the CNS, suggesting that it might be a treatment alternative for demyelination, according to our findings. Bergenin, being a natural substance, might be a potential alternative as a therapy for MS if additional research shows it to be effective. Many plant-based substances are used as pharmaceuticals to treat long-term ailments, and they have no detrimental side effects. It can also be evaluated for its potential use as first-line therapy for Multiple sclerosis. In this in-silico research, we recommend that more in vitro and in vivo investigations in various animal models be conducted to determine the effect of Bergenin as a neuroprotective agent against demyelination.

Funding: This research work receives no funding or financial assistance from any individual or organization.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgment: We wish to thank the HOD, Department of Bioinformatics, School of Bio and Chemical Engineering, Sathyabama Institute of Science and Technology, Chennai, 600 119, Tamil Nadu, India for its facilities and guidance throughout the course of work.

Authors Contributions: All the authors have contributed equally

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