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Research Article

Pharmacokinetics and Molecular Docking Studies of Sinapaldehyde and MCM7 Protein against Meier-Gorlin Syndrome

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Abstract

Objective: The objective of this study to investigate the MCM7 protein in contrast to Meier-Gorlin Syndrome which contains most of the ORC1, ORC4, ORC6, CDT1, and CDC6 causative genes in the preinitiation complex disruptions.

Methods: Sinapaldehyde and MCM7 were retrieved from Protein Data bank and PubChem database in the format of PDB and SDF format. Further, SDF format was converted to PDB format using Biovia Discovery Studio visualizer. Sinapaldehyde was subjected to pharmacoinformatics study as well as Molecular Docking analysis to find out the best anti-Gorlin potential.

Results: Sinapaldehyde showed the -5.9kcal/mol binding affinity against MCM7 protein which considers to be a better candidate drug molecule against Meier-Gorlin Syndrome and validated using Pharmacokinetics mechanism.

Conclusion: Molecular Docking studies and ADMET analysis showed the inhibitory activity of Sinapaldehyde with respect to Meier-Gorlin Syndrome and related pathway analysis and can be better compound for in vitro studies for future perspectives.

Keywords: MCM7; ADMET; Sinapaldehyde; Meier-Gorlin Syndrome

Introduction

Meier-Gorlin Syndrome (MGS) is an autosomal recessive syndrome characterized by short stature, growth retardation, small mouth, small ears and ear canals, microcephaly, patellar anomalies like small kneecaps [1]. Meier-Gorlin syndrome is a kind of primordial dwarfism and it is strongly associated with the preinitiation complex disruption. Few other symptoms include small head size, problem in feeding, abnormalities in the respiratory tract. Females who have this syndrome may have underdeveloped breasts. The mutated genes (ORC1, ORC4, ORC6, CDT1, and CDC6) encoding constituents of the pre-replication complex (PRC) are found to be one of the primary causes in patients with MGS [1]. In most cases, this syndrome is inherited to the child as an autosomal recessive pattern. Diagnosis of some major diseases can be challenging, even the doctors for such cases look at the patient's medical history, what symptoms the patient has, the laboratory results, etc. to diagnose that patient. Based on the symptoms and signs, MGS is diagnosed through genetic testing. Most people, who are affected by MGS, can expect normal life longevity. In rare cases, the severity of this syndrome is too harsh such as abnormal breathing in infancy or later in life and the life span of patient also depends on how severe the disease is [2]. MCM7 helicase is a heterohexameric complex which has some essential roles and in the early stages of DNA replication processes it is a part of both pre-replication and pre-initiation complexes. It is confirmed that variants in MCM7 protein are deleterious and through interfering with the MCM complex formation, it has an impact inefficiency of S phase progression. The MCM7 protein is encoded by the MCM7 gene which is one of the minichromosome maintenance proteins which is highly responsible for the eukaryotic genome replication. Replication fork is formed by the hexameric protein complex. The CDK4 associated with this protein regulates the binding of MCM7 with the tumour suppressor protein RB1 [3].

Materials and Methods

Preparation of ligand

The required information and structures of our ligand, sinapaldehyde, were retrieved from the PubChem database which was later used for molecular docking simulations with the receptor MCM7 [9-11]. The structures were downloaded from PubChem in Standard Data Format (SDF) which was converted into Protein Data Bank (PDB) format using PyMol version 2.5.1 [4-6].

Receptors

We have used MCM7 receptors against the selected ligand sinapaldehyde to inhibit the activity of Mier-Gorlin Syndrome.

Homology modelling

We have used SWISS-MODEL for the homology modelling of the MCM7 receptor [12-14]. The FASTA sequence of the receptor was retrieved from the NCBI database to prepare the template model [15,16]. A total of 8 models were retrieved from the server. We have selected the template (Model 01(MCM7)) which had a 100% sequence identity with respect to the chosen template.

ADMET analysis

We have used the drug discovery tool, SwissADME for the

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analysis of ADMET, physicochemical properties, pharmacokinetics and drug likeliness. The SwissADME analysis is based on the "Five Rules of Lipinski" which follows some standard criteria such as molecular mass, lipophilicity, hydrogen bond acceptors and donors. This was performed to check the oral feasibility of the drug in humans [17,18].

Boiled-egg

SwissADME server was used for the Boiled-Egg structure analysis. The Boiled-Egg plot is used to evaluate the gastrointestinal absorption and brain penetration through the Blood-Brain Barrier of the drug. The white zone indicates a high likelihood of passive absorption through the gastrointestinal system, while the yellow region (yolk) indicates a high likelihood of brain penetration [17-19].

Molecular docking analysis

Molecular docking was performed using virtual software PyRx [7,8]. The purpose behind performing molecular docking is to predict the possible interactions of the sinapaldehyde with the targeted MCM7 protein receptor. PyRx, which is virtual screening software, uses Vina and AutoDock 4.2 as docking software from which the binding affinity and the Root Mean Square Deviation (RMSD) values were considered.

After docking, we have visualized the structure and the interactions using the visualization tool, Biovia Discovery Studio Visualizer (DSV) version 21.1.0 [20].

Results and Discussion

Ligand

The information related to the sinapaldehyde was retrieved from the PubChem database and the screening of it was done using Biovia Discovery Studio. The structure of the ligand was downloaded in Standard Data Format (SDF) and it was converted into PDB format for further docking purposes (Figure 1).

Receptor

See Figure 2.

ADMET analysis

According to the Lipinski rule, there is zero violation as molecular weight was is less than 500, H-bond donors are less than 5, H-bond acceptors are less than 10 and molar refractivity is in the range of 40 to 130. As the results are in the acceptable range, we could predict that

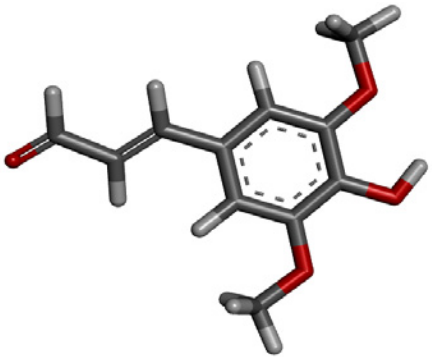

Figure 1: Sinapaldehyde (3D).

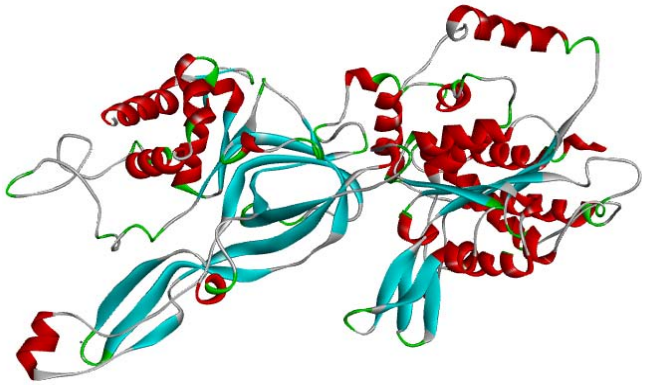

Figure 2: Receptor-MCM7.

Table 1: Physicochemical Properties.

Formula	$C_{11}H_{12}O_4$
Molecular Weight	208.21g/mol
Num. heavy atoms	15
Num. arom. heavy atoms	6
Fraction Csp3	0.18
Num. rotatable bonds	4
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	56.55
TPSA	55.76 Å^2

Table 2: Pharmacokinetics.

GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.58cm/s

Table 3: Druglikeness.

Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

sinapaldehyde is safe for human use (Table 1-3).

Boiled-egg

From the boiled-egg structure, it could be predicted that the molecule (sinapaldehyde) has a high probability to permeate through the Blood-brain barrier as it is present in the yellow (yolk region) and

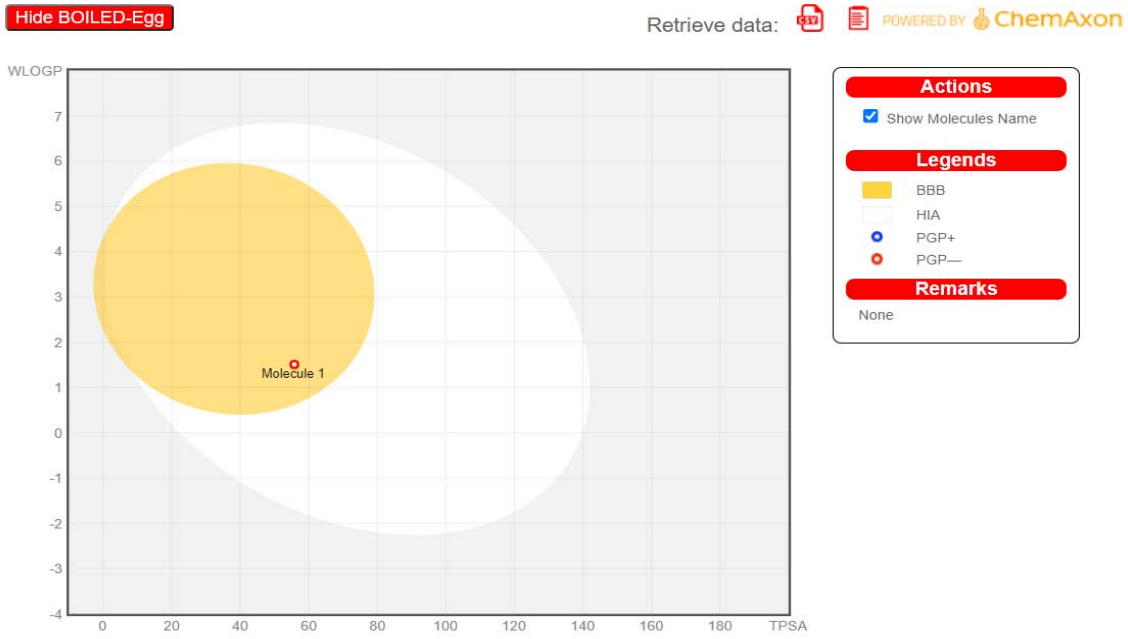

Figure 3: Hide Boiled Egg.

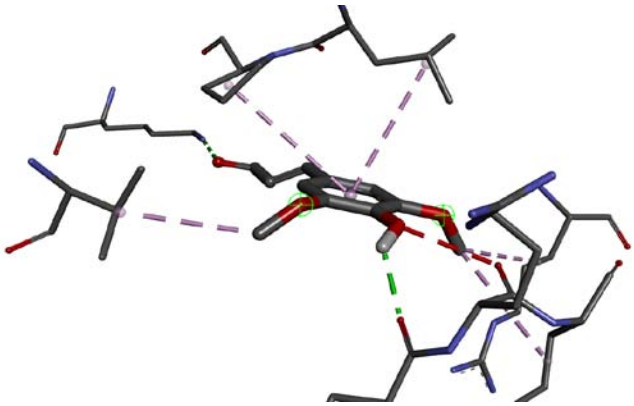

Figure 4: Ligand interactions.

hence it could be considered as a brain penetrant. Moreover, as it is not actively effluxed by P-glycoprotein, that is, PGP - (red dot), it could be predicted as a toxic molecule (Figure 3).

Molecular docking analysis

The molecular docking results show that sinapaldehyde has a good binding affinity towards MCM7. Moreover, from the Root Mean Square Deviation (RMSD), it has been found that all the transformations have been done and the protein (MCM7) is completely binding with the ligand (Table 4). By analysing the results, it could be predicted that it would be suitable for the treatment of Meier-Gorlin syndrome (Figure 4 and 5).

Conclusion

The aforementioned ligand, sinapaldehyde showed better interaction with the MCM7 receptor. By performing molecular docking of sinapaldehyde and MCM7 receptor we have found out

Table 4: Molecular Docking Analysis.

Complex	Binding affinity (kcal/mol)	RMSD lower bound	RMSD upper bound
MCM7-Sinapaldehyde	-5.9	0.0	0.0

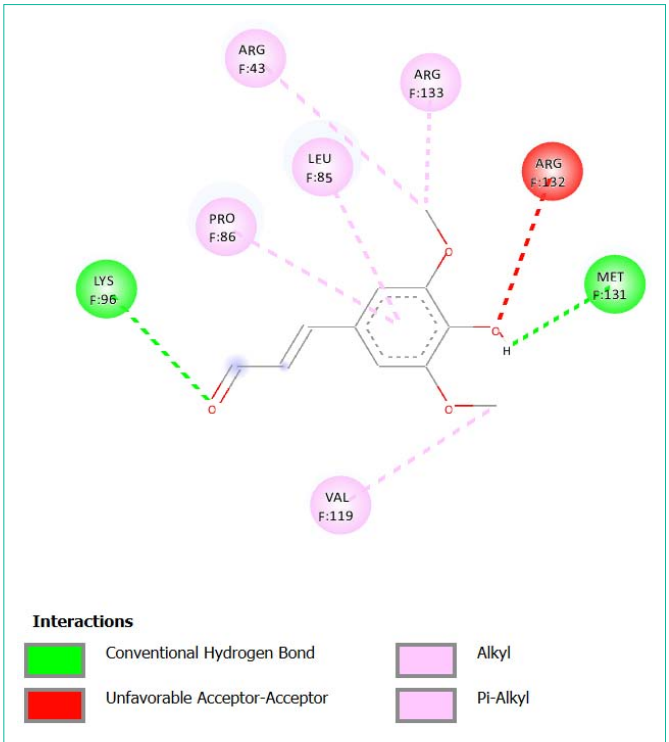

Figure 5: 2D Diagram.

the inhibitory activity of sinapaldehyde against the MCM7 receptor. Sinapaldehyde has the ability to inhibit the activity of MCM7 in the regular pathways with the binding affinity of -5.9kcal/mol.

For understanding the therapeutic purposes we have done all the pharmacological studies followed by molecular docking. Hence, we can conclude that the ligand we have used in this study paves a way for the treatment of the Mier-Gorlin Syndrome and has also shown promising outcomes for further studies.

Declaration

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Author's contribution: All authors contributed equally to manuscript.

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