GLOBAL JOURNAL
OF MEDICAL RESEARCH - K: INTERDISCIPLINARY
Volume 26 | Issue 1 | 2026 Article ID: GJMR-154713 Language: English

CATALOGING
NLM • WL 470

An in-Silico study – Targeting a Genetic Intellectually Different ability's Therapy, through Phytochemicals

Article Record

Dr. Ayushi[§ϑ*]
Research scholar
*Corresponding Author

§ Department of Biotechnology, Shri Ramswaroop Memorial University, Lucknow-Barabanki, India (**OA**)

RECEIVED	ACCEPTED	ONLINE PUBLISHED	PUBLISHED	PEER REVIEW
2026-01-27	2026-02-10	2026-02-23	2026-06-23	Double Blind

Abstract

People with 'intellectually different ability or intellectual disability (ID)' have neurodevelopmental deficits, which is shown by, limitations in 'intellectual functioning' and 'adaptive behavior'. 'Fragile X syndrome' is the common genetic cause of 'Intellectually different ability (ID)'. Therefore in this in-silico research, a protein named 'mGluR5' was targeted for the therapy of ID in Fragile X Syndrome. In Fragile X syndrome, due to mutation in FMR1 gene, there's lack of FMRP (Fragile X Mental Retardation Protein), resulting in unimpeded (lack of inhibition by FMRP) activity of 'mGluR5', which leads to aberrant dendritic development with mis-signalling, This results in ID, Autism and Psychopathology. As an attempt, for overcoming this problem of ID seen in the patients of Fragile X syndrome, in this research, 'mGluR5' was targeted by 19 different phytochemicals, collected from IMPPAT 2.0 databse. This study was done with the aid of multiple bioinformatics tools and biological databses, namely 'RCSB-PDB', 'BIOVIA Discovery Studio', 'PubChem', 'CACTUS Online SMILES translator', 'CB-Dock' and 'pkCSM'. The conclusion of this research, compared with 'Fenobam (already reported against mGluR5) was that, 'beta-Bisabolene' and 'Cirisilineol' have relatively more probability to serve as therapeutic compounds against 'mGluR5', as compared to "Platainoside-B', 'Orientin' and other phytochemicals in the list of 19 phytochemicals studied in this research. However, different results may or may not show up in 'in-vitro' or 'in-vivo' researches.

Intellectually different ability (Intellectual disability) | Phytochemicals | mGluR5 | Fragile X syndrome

AI USE STATEMENT
No generative AI was used for analysis or results.

FUNDING
No external funding was declared for this work.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY
Not applicable for this article.

ETHICS
No ethics committee approval was required for this article type.

CONSENT
Not applicable for this article.

TRIAL REG.
Not applicable.

Crossref DOI: 10.34257/GJMRK154713

How to Cite: Ayushi (2026). An in-Silico study – Targeting a Genetic Intellectually Different ability's Therapy, through Phytochemicals. Global Journal of Medical Research, 26(1), 1-7. DOI: 10.34257/GJMRK154713

AR Experience Web Page DOI

Print ISSN 0975-5888
Online ISSN 2249-4618

Under the strict compliance and defined process of

METADATA CONTINUATION

AUTHOR CONTACT QR LEDGER

Dr. Ayushi§ϑ*

ARCHIVAL RECORD

GJMR · Vol 26 · Issue 1 · 2026

Article ID GJMR-154713 · DOI 10.34257/GJMRK154713

Print ISSN 0975-5888 · Online ISSN 2249-4618

Global Journal of Medical Research - Section K
GJMR Volume 26 Issue 1

An in-Silico study – Targeting a Genetic Intellectually Different ability's Therapy, through Phytochemicals

Dr. Ayushi[§ϑ*]

Affiliations
§ Department of Biotechnology, Shri Ramswaroop Memorial University, Lucknow-Barabanki, India (OA)

Qualifications / Designations
ϑ Research scholar

Abstract

People with 'intellectually different ability or intellectual disability (ID)' have neurodevelopmental deficits, which is shown by, limitations in 'intellectual functioning' and 'adaptive behavior'. 'Fragile X syndrome' is the common genetic cause of 'Intellectually different ability (ID)'. Therefore in this in-silico research, a protein named 'mGluR5' was targeted for the therapy of ID in Fragile X Syndrome. In Fragile X syndrome, due to mutation in FMR1 gene, there's lack of FMRP (Fragile X Mental Retardation Protein), resulting in unimpeded (lack of inhibition by FMRP) activity of 'mGluR5', which leads to aberrant dendritic development with mis-signalling, This results in ID, Autism and Psychopathology. As an attempt, for overcoming this problem of ID seen in the patients of Fragile X syndrome, in this research, 'mGluR5' was targeted by 19 different phytochemicals, collected from IMPPAT 2.0 databse. This study was done with the aid of multiple bioinformatics tools and biological databses, namely 'RCSB-PDB', 'BIOVIA Discovery Studio', 'PubChem', 'CACTUS Online SMILES translator', 'CB-Dock' and 'pkCSM'. The conclusion of this research, compared with 'Fenobam (already reported against mGluR5) was that, 'beta-Bisabolene' and 'Cirisilineol' have relatively more probability to serve as therapeutic compounds against 'mGluR5', as compared to "Platainoside-B', 'Orientin' and other phytochemicals in the list of 19 phytochemicals studied in this research. However, different results may or may not show up in 'in-vitro' or 'in-vivo' researches.

Keywords: *Intellectually different ability (Intellectual disability), Phytochemicals, mGluR5, Fragile X syndrome*

*** Corresponding Author**
Dr. Ayushi

DOI
10.34257/GJMRK154713

1. Introduction

Intelligence' is the general *mental* ability for reasoning, problem-solving and learning. This mental ability integrates other cognitive abilities and works also, such as, perception, attention, memory, language or planning. Neuroimaging studies have generally supported that, a frontoparietal network is relevant for intelligence. This same network is also found to be associated with other cognitive functions, such as, perception, storage of shortterm memory and language. This network has a distributed nature and is involved in different cognitive abilities and functions. This fact clearly explains that, the nature of intelligence is 'integrative'. [1].

Jung and Haier looked into 37 structural and functional studies on neuroimaging, which were published between 1988 and 2007. They found some commonalities in their study. On the basis of these commonalities, they proposed 'Parieto-Frontal Integration Theory (PFIT)'.

Given below, is somewhat easy explanation of our Brain's functioning, associated with intelligence -

1. In the first stage of this process, occipital and temporal areas process sensory information. The extrastriate cortex (Broadmann areas (BAs) – 18 and 19) and the fusiform gyrus (BA37), are involved with recognition, imagery and elaboration of visual inputs. Wernicke's area is utilized for analyzing and elaborating syntax of auditory information.
2. Parietal BAs 39 i.e. angular gyrus, BAs 40 i.e. supramarginal gyrus, BAs 7 i.e. superior parietal lobule are utilized for integration and abstraction of the sensory information. This is involved in the second stage of process.
3. In the third stage of this process, the parietal areas interact with the frontal lobes. This interaction leads to - solving problems, evaluation and testing of hypothesis. Frontal BAs 6, 9, 10, 45, 46 and 47 are involved in this stage.
4. Then, in the fourth stage of this process, the anterior cingulate (BA 32), is involved in selection of response and inhibiting the alternative responses, after above three stages of this process.

Thus, we can say that, frontal, parietal, temporal and occipital areas are involved in the above-mentioned process. However, Jung and Haier say that, it is not necessary that, all these areas are equally essential for every individual's intelligence. Regions of brain of the dorsolateral prefrontal cortex, such as BAs 9, 45, 46 and 47; and, the parietal cortex, such as BAs 7 and 40, can be considered as most important parts for the intelligence of a human being. [1, 2].

Thus, we can say that, frontoparietal network of our brain maybe necessary for intelligence. But, this network is also relevant for working memory. [1, 3]. This was studied by Gray et al. [1, 4]. Commonality between intelligence and working memory was also discovered during the studies on animals, by Matzel and Kolata. [1, 5].

1.1. Intellectually Different Ability (Intellectual Disability)

People with 'intellectually different ability or intellectual disability (ID)' have neurodevelopmental deficits. This neurodevelopmental deficit is shown by limitations in 'intellectual functioning' and 'adaptive behavior'. These disabilities begin in childhood, and symptoms appear before the age of 22. Before, studying ID in more detail, let us take a look at the concept of 'Intellectual functioning'. [6].

'Intellectual functioning (IF)' is also called 'Intelligence'. It includes multiple mental activities, such as - logical reasoning and practical intelligence (problemsolving), ability to learn things, verbal skills, etc. IF expresses itself through multiple capabilities, behaviors, thoughts and emotions. We can also say that, IF is the global ability which helps us to understand and interact with reality. It is measured in terms of 'Intelligence quotient (IQ)'. To measure this, IQ tests are taken. The median of this test is 100 and standard deviation is 15. If the score of this test is 70 or below, that is the indication of ID. [6].

Adaptive behavior disabilities are expressed as lack of competence in social, conceptual and practical skills. These skills are quite poor in the people having ID. [6].

1.2. Few Genetics and Environmental Factors of ID

ID can develop due to various genetic mutations and diseases, or, environmental reasons. The genetic abnormalities responsible for ID could be mutation in a gene, copy number variation, or chromosomal abnormality that cause inborn errors of metabolism, defect in neurodevelopment and neurodegeneration. Environmental reasons can be, maternal exposure to toxin or infectious agents, uncontrolled maternal medical conditions, complications in parturition, and post-natal trauma and exposure to toxin/infectious agents. The most common environmental reason for ID, which can be prevented is 'fetal alcohol syndrome'. 'Down's syndrome' is the most common chromosomal cause for ID, and, the most common genetic cause for ID is 'Fragile X syndrome'. [6].

In 'Fragile X syndrome', there's a single gene mutation in the 'FMR1' gene. FMR1 gene is actually a transcription factor of several genes (hundreds of genes) expressed in the 'Central Nervous System (CNS)' and its disruption causes 'ID' and 'behavioral disturbance and seizure.' [6, 7].

In 'Rett Syndrome', neurodegeneration leads to ID. It is an X-linked dominant degenerative condition, which shows up only in females, secondary to mutation of the 'MeCP2 gene'. In the patients of Rett Syndrome, at the substantia nigra cerebral atrophy occurs, which causes defects in the dopaminergic nigrostriatal pathway. This cerebral atrophy begins at the age of 6 to 18 months. [6, 8].

When fetus is exposed to alcohol, that exposure inhibits the production of retinoic acid, which is a necessary signaling molecule for nervous system's development. Consumption of even a small amount of alcohol in any trimester of gestation period (pregnancy), leads to the development of fetal alcohol syndrome. [6, 9]. Exposure to opioids, cocaine and teratogenic medications, may also be the cause of 'Intellectual disability'. [6].

Rubella and HIV are few commonly known infectious agents, which can cause Intellectual Disability. When the pregnant mother is infected with rubella, during the initial trimester of gestation period, $10 - 15\%$ of the time, it leads to 'Intellectual Disability'. This probability can be above 15% , if this infection occurs, during the first month of pregnancy. If the pregnant mother is vaccinated, then this infection of rubella can be prevented. [6, 10]. HIV in infants may also lead to encephalopathy, seizures and Intellectual disability within the first year of life secondary to microcephaly, immunosuppression and *Pneumocystis jiroveci pneumonitis* (PCP) infection. This HIV may get transferred vertically from mother to infant. [6, 11].

Few uncontrolled maternal medical conditions during the gestation period may also increase the risk of ID, such as, Pregnancy hypertension, Asthma, urinary tract infection, pre-pregnancy obesity, and pregestational Diabetes. [6, 12]. Some other medical conditions, such as, uncontrolled maternal Diabetes, malnutrition and obstetrical complications, which causes anoxia, may also cause ID. [6, 13]. ID can be acquired during early childhood, due to infections (maybe Encephalitis or Meningitis), head trauma, asphyxia, intracranial tumor, malnutrition and exposure to toxic substances. [6, 14].

1.3. Fragile X Syndrome - Science Behind ID

This is a common genetic cause of ID, which affects 1 in 4,000 people. The Fragile X protein, FMRP (Fragile X Mental Retardation Protein), regulates the dendritic growth, with the GABAergic system being especially sensitive. Lack of FMRP (Fragile X Mental Retardation Protein), results in unimpeded (lack of inhibition by FMRP) activity of 'mGluR5', which leads to aberrant dendritic development with mis-signalling, This results in ID, Autism and Psychopathology. [15, 16]. Trial against 'mGluR5' has also been performed, with the motive to replace the inhibitory effect of the missing FMRP protein. Phase 1 trial of 'Fenobam' has suggested a promising efficiency based on a single dose. [15, 17]. Additionally, the antibiotic 'Minocycline' has also shown inhibition of mGluR5 receptor and some efficacy. [15, 18, 19].

In this in-silico research, 'Intellectually different ability (Intellectual disability)' due to 'Fragile X syndrome' has been targeted by the phytochemicals, to obtain a few partially validated compounds against ID.

Now, let us take a look at, some of the medicinal plants, which are positively effective on our Brain, from which the phytochemicals have been collected for this research.

1.4. Medicinal Plants - on our Brain

1. *Bacopa monnieri*: This plant is also known as 'Brahmi' or 'water hyssop'. It is used in Ayurveda for its ability to enhance memory and control the level of sugar in the blood. [20, 21]. It contains various active compounds such as alkaloids, saponins and cucurbitacins, which exhibit different biological activities. It has the potential to treat multiple brain-related diseases, such as Alzheimer's disease, Parkinson's disease, Attention Deficit Hyperactivity Disorder and Depression. [21].

2. *Withania somnifera*: This plant is also known as 'Ashwagandha' [20, 22]. This is also known as 'Indian ginseng' or 'Indian winter cherry'. The name 'Ashwagandha' is derived from two words - 'ashwa', which means 'horse', and, 'gandha', which means 'fragrance', refers to the smell or aroma of this plant's fresh roots. It is said that, when someone consumes its roots, that person gains similar power as the horse. [22, 23]. Since ancient time, it has been traditionally used in Ayurvedic medicine, which enhances the strength of 'Nervous system'. It can provide multiple benefits to our brain, such as - Ability to treat neurodegenerative disorders, Obsessive Compulsive Disorder, Alcohol withdrawal syndrome, and, anti-inflammatory effects. [22].

3. *Centella asiatica*: This plant is also known as 'Mandukparni'. [20]. This plant has been used for centuries in Ayurvedic and Chinese medicine, for its cognitive benefits. [24]. Few modern scientific studies, which have been performed on rodents, and, in human subjects, have shown that, whole *Centella asiatica* extracts and some of its active compounds, exhibit the ability to enhance cognition or neurotropic properties. [24, 25, 26, 27, 28, 29, 30]. Therapy given by '*Centella asiatica*' has also been found to reduce oxidative stress and mitochondrial dysfunction in rodents. It also exhibit neuroprotective potential in chemically induced Alzheimer's disease. [24, 31, 32, 33, 34, 35].

4. *Ocimum sanctum*: This plant is also known as '*Ocimum tenuiflorum*'. Traditionally, it is also known as 'Holy basil' or "Tulsi". [20, 36]. This medicinal plant has the potential to provide many different health benefits. Various scientific researches have shown that this medicinal plant can exhibit anti-stress potential, but with higher doses. Extract of this plant was found to inhibit the release of cortisol. It was also found to exhibit the significant CRF1 receptor antagonist activity. Thus, the extract of this plant was found to effectively manage stress. This effectiveness could be due to, either inhibition of cortisol release, or, CRF1 receptor antagonist effect. [20, 37].

In this in-silico study, 19 different phytochemicals are collected from these plants and have been targeted in-silico against 'mGluR5'. Now, let us take a look at, a few tools and biological databases, utilized in this in-silico study.

1.5. Tools and Databases

1. IMPPAT 2.0 Database: 'IMPPAT 2.0' is an enhanced and expanded database. It has information on 4,010 Indian medicinal plants, 17,967 phytochemicals, and, 1,095 therapeutic uses. It contains the information about the associations at the level of plant parts. Overall, it is a manually curated database, which contains phytochemical atlas of Indian medicinal plants. [38]. In this research, this database has been used for the collection of phytochemicals, to be utilized as ligands.

2. Protein Data Bank (RCSB-PDB): It stands for 'Research Collaboratory for Structural Bioinformatics Protein Data Bank.' [39, 41]. It is an open access database of Biology which shares the 3-Dimensional structures of proteins. [40, 41]. It was established in 1971 with 7 structures. But, over the period of time it became possible to access more than 113,000 entries of natural and designed macromolecules. More than 84,000 of those macromolecules are complexed with small chemical components, such as solvent, ions, cofactors, inhibitors and drugs. This database was originally designed for the structural biology community, but, over the period of time, other professionals also began to use it. [41]. In this research, this database has been used to visualize and obtain the 3-Dimensional structure of 'mGluR5'.

3. https://projectgemmi.github.io/wasm/convert/cif2pdb.html: In this research, this link was used to convert .cif files to .pdb files.

4. BIOVIA Discovery Studio: This tool is mainly used for protein cleaning. However, in this research the two structures of α-synuclein didn't require cleaning at all.

5. PubChem: It is a public repository, which provides information about various chemical substances. It is a database of NCBI. It was launched in 2004. It is a component of Molecular Libraries Roadmap Initiatives of US National Institute of Health. Since years, this database has been serving as a resource for chemical information for the scientific research community. [42]. In this research, PubChem has been used to study the chemistry of ligands, and, download the 3-Dimensional structures of the ligands in '.sdf' format.

6. CACTUS Online SMILES Translator: It belongs to NCI/CADD group, NIH-National Cancer Institute. [43]. In this research, this tool has been used to convert the .sdf files of ligands into .pdb files, so that those 3D structures of ligands can be used for docking.

7. CB-Dock: It is a user-friendly web server for blind docking. It predicts binding modes without information about binding sites. It predicts binding sites of a given protein and calculates the centres and sizes with a new curvature-based cavity detection approach. It performs docking with 'AutoDock Vina'. It provides an interactive 3-Dimensional visualization of results, and is available free of cost at http://clab.labshare.cn/cb-dock/. [44]. In this research, this tool has been used for the blind docking of 19 phytochemicals against the 3-Dimensional structure of 'mGluR5'.

8. pkCSM Tool: It is a novel approach for the prediction of ADMET properties. It uses graph-based signatures to develop the predictive models of central ADMET properties. [45]. In this research, this tool has been used to analyse the Lipinski's rule of 5 of each shortlisted phytochemical and their computations for absorption, distribution, metabolism, excretion and toxicity.

2. Methodology

1. Target Identification, Retrieval of 3-Dimensional Structure and Protein Cleaning: In the first step of this research, through literature survey, 'mGluR5' was identified as the suitable target protein, to target "intellectually different ability (intellectual disability)", which is a symptom of "Fragile X syndrome". After the identification of 'mGluR5' as target, 3-Dimensional structure of 'mGluR5' having PDB ID - '6FFH' was downloaded from 'RCSB-PDB' database. After download, this '.cif' file was converted into '.pdb' format using https://projectgemmi.github.io/wasm/convert/cif2pdb.html. Then, this 3-Dimensional structure of 'mGluR5' with '.pdb' format was cleaned using 'Discovery Studio'.

2. Collection of ligands: Medicinal plants, which are positively effective on our brain and have therapeutic potential to treat brain-related problems were identified through literature survey, as mentioned above. In this step, a list of 19 phytochemicals were collected from 'IMPPAT 2.0 database', to be utilized as ligands in this research. These phytochemicals were collected from *Bacopa monnieri*, *Withania somnifera*, *Centella asiatica*, and *Ocimum sanctum* (*Ocimum tenuiflorum*).

3. CB-Dock analysis of 'Fenobam' and 'Minocycline' for reference: In this step, I analysed the docking affinity of 'Fenobam' and 'Minocycline' against 'mGluR5' for my reference, as these phytochemicals have been found to be quite effective against 'mGluR5', as mentioned above. It was decided that

in this in-silico research, the docking affinity of my list of phytochemicals will be compared with the docking affinity of 'Fenobam' and 'Minocycline', considering both of them as standards.

4. CB-Dock analysis of 19 ligands: In this step, 19 phytochemicals of the list were docked against 'mGluR5' and their minimum vina scores and cavity size were recorded. As decided, their docking results were compared with that of 'Fenobam' and 'Minocycline'. On the basis of this comparison, a few phytochemicals from the list were shortlisted. The criteria for this comparison was whether they are equivalent or more negative in terms of vina score, as compared to 'Fenobam' and 'Minocycline' or not. Those phytochemicals or ligands, which showed equivalent or more negative vina scores in the same cavity size as 'Fenobam' were considered more suitable for further research and were shortlisted for ADMET analysis.

5. Analysis of Lipinski's rule of 5 of the shortlisted ligands: In this step, Lipinski's rule of 5 was analysed for each shortlisted phytochemical (ligand), to check whether they are violating or not violating Lipinski's rule of 5. The shortlisted ligands were checked for whether:

6. Detailed ADMET analysis: In this step, Absorption, Distribution, Metabolism, Excretion and Toxicity were computed and analysed for the shortlisted compounds to understand their pharmacokinetics in detail.

3. Results

3.1. Cleaned 3-Dimensional Structure of Target Protein

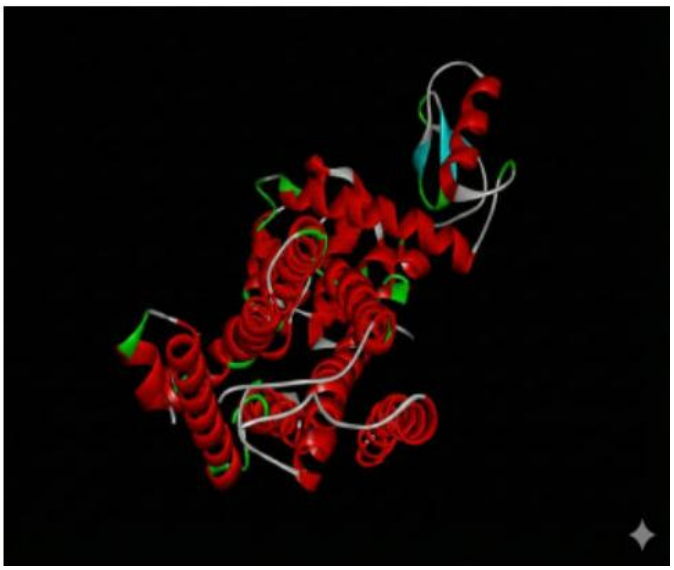

Figure 1. 3-Dimensional cleaned structure of 'mGluR5'. [47]

3.2. Collection of Ligands from IMPPAT 2.0 Database

List of phytochemicals, collected from IMPPAT 2.0 database, utilized as ligands. [52].

Table 1. List of phytochemicals collected from IMPPAT 2.0 database. [52]

S. No.	Plant source (Plant part)	Phytochemicals
1.	*Bacopa monnieri* (Leaf)	Apigenin-7-O-glucuronide
2.	*Bacopa monnieri* (Whole plant)	Plantainoside B
3.	*Withania somnifera* (Leaf)	Hygrine
4.	*Withania somnifera* (Leaf)	Cuscohygrine
5.	*Centella asiatica* (Aerial part)	Beta-Bisabolene
6.	*Centella asiatica* (Aerial part)	2-Heptenal
7.	*Centella asiatica* (Aerial part)	E-(2)-Octenal
8.	*Centella asiatica* (Aerial part)	alpha-Pinene
9.	*Centella asiatica* (Aerial part)	beta-Pinene
10.	*Centella asiatica* (Aerial part)	Nerol
11.	*Ocimum tenuiflorum* (Leaf)	Samaderine-E
12.	*Ocimum tenuiflorum* (Leaf)	Eugenol
13.	*Ocimum tenuiflorum* (Leaf)	E-alpha-Bisabolene
14.	*Ocimum tenuiflorum* (Leaf)	Cirsilineol
15.	*Ocimum tenuiflorum* (Leaf)	Orientin
16.	*Ocimum tenuiflorum* (Leaf)	Eupalitin
17.	*Ocimum tenuiflorum* (Leaf)	Ascorbic acid
18.	*Ocimum tenuiflorum* (Leaf)	Decanal
19.	*Ocimum tenuiflorum* (Leaf)	Cadinane

3.3. CB-Dock Analysis of Standards or References - Fenobam and Minocycline

When 'Fenobam' was docked against 'mGluR5', it showed the minimum vina score of -8.2 in the cavity size of 2432. On the other hand, when 'Minocycline' was docked against 'mGluR5', it showed the minimum vina score of -8.2 in the cavity size of 334. [53].

3.4. CB-Dock Analysis of Ligands Against mGluR5

Table 2. CB-Dock analysis of ligands against 'mGluR5'. [53]

S. No.	Phytochemicals	Binding Energy (kcal/mol)	Cavity Size (Å^3)
1.	Apigenin-7-O-glucuronide	-8.6	398
2.	Plantainoside B	-8.2	2432
3.	Hygrine	-5.4	343
4.	Cuscohygrine	-7.5	2432
5.	Beta-Bisabolene	-9.0	2432
6.	2-Heptenal	-4.7	2432
7.	E-(2)-Octenal	-6.1	2432
8.	alpha-Pinene	-5.5	2432
9.	beta-Pinene	-5.5	2432
10.	Nerol	-7.1	2432
11.	Samaderine-E	-8.2	398
12.	Eugenol	-6.3	2432
13.	E-alpha-Bisabolene	-7.3	2432
14.	Cirsilineol	-8.7	2432
15.	Orientin	-8.2	2432
16.	Eupalitin	-7.8	2432
17.	Ascorbic acid	-6.6	2432
18.	Decanal	-6.4	2432
19.	Cadinane	-7.7	2432

3.5. pkCSM Analysis of Lipinski's Rule of 5 of Shortlisted Ligands

Table 3. Lipinski's Rule of 5 Analysis of 'Platainoside B'. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	478.45	No
H-bond donor	7	Yes
H-bond acceptor	11	Yes
LogP	0.1323	No
Rotatable bonds	8	No

Table 4. Lipinski's Rule of 5 Analysis of 'beta-Bisabolene'. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	204.357	No
H-bond donor	0	No
H-bond acceptor	0	No
LogP	5.0354	Slight
Rotatable bonds	4	No

Table 5. Lipinski's Rule of 5 Analysis of 'Cirsilineol'. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	344.319	No
H-bond donor	2	No
H-bond acceptor	7	No
LogP	2.897	No
Rotatable bonds	4	No

Table 6. Lipinski's Rule of 5 Analysis of 'Orientin'. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	448.38	No
H-bond donor	8	Yes
H-bond acceptor	11	Yes
LogP	-0.2027	No
Rotatable bonds	3	No

3.6. Detailed ADMET Computation and Analysis

Table 7. Detailed ADMET Analysis of shortlisted ligands from pkCSM tool. (Part 1: Absorption and Distribution) [54]

Category	Model Name	Platainoside B	Beta-Bisabolene	Cirsilineol	Orientin
Absorption	Water solubility (log mol/L)	-2.992	-6.133	-3.749	-3.164
	CaCO2 permeability (log Papp in 10^{-6} cm/s)	-0.048	1.408	1.247	-0.794
	Intestinal absorption (Human, %)	26.868	94.094	89.153	44.19
	Skin permeability (log Kp, cm/hr)	-2.735	-1.222	-2.747	-2.735
	P-glycoprotein substrate	Yes	No	Yes	Yes
	P-glycoprotein I inhibitor	No	No	No	No
	P-glycoprotein II inhibitor	No	No	Yes	No
Distribution	VDss (Human, log L/kg)	0.872	0.633	-0.336	0.164
	Fraction unbound (Human, Fu)	0.362	0.233	0.158	0.102
	BBB permeability (log BB)	-1.682	0.778	-0.789	-1.934
	CNS permeability (log PS)	-4.195	-2.101	-3.187	-4.758

Table 8. Detailed ADMET Analysis of shortlisted ligands from pkCSM tool. (Part 2: Metabolism, Excretion, and Toxicity) [54]

Category	Model Name	Platainoside B	Beta-Bisabolene	Cirsilineol	Orientin
Metabolism	CYP2D6 substrate	No	No	No	No
	CYP3A4 substrate	Yes	No	Yes	No
	CYP1A2 inhibitor	No	No	Yes	No
	CYP2C19 inhibitor	No	No	Yes	No
	CYP2C9 inhibitor	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No
	CYP3A4 inhibitor	No	No	No	No
Excretion	Total clearance (log ml/min/kg)	-0.123	1.458	0.639	0.521
	Renal OCT2 substrate	No	No	No	No
Toxicity	AMES toxicity	No	No	No	No
	Max tolerated dose (human, log mg/kg/day)	0.199	0.280	0.554	0.769
	hERG I inhibitor	No	No	No	No
	hERG II inhibitor	No	No	No	Yes
	Oral Rat Acute Toxicity (LD50, mol/kg)	2.651	1.597	2.258	3.003
	Oral Rat Chronic Toxicity (LOAEL, log mg/kgbw/day)	3.367	1.339	0.953	3.342
	Hepatotoxicity	No	No	No	No
	Skin sensitisation	No	Yes	No	No
	T.Pyriformis toxicity (log ug/L)	0.285	1.928	0.361	0.285
	Minnow toxicity (log mM)	3.858	0.082	0.757	5.809

4. Discussion

This research began with the literature survey to identify the target protein, and, medicinal plants, which can cure brain-related problems, to identify partially validated therapeutic agents at in-silico level, to treat 'Intellectually different ability (Intellectual disability)', due to 'Fragile X syndrome'. 'mGluR5' was identified as the suitable protein to be targeted, as due to lack of 'FMRP' activity, as a result of mutation in 'FMR1' gene, unimpeded (lack of inhibition by FMRP) activity of 'mGluR5', which leads to aberrant dendritic development with mis-signalling. This results in ID, Autism and Psychopathology. Then, 19 different phytochemicals were collected from *Bacopa monnieri*, *Withania somnifera*, *Centella asiatica*, and *Ocimum sanctum* (*Ocimum tenuiflorum*) after gathering knowledge about their therapeutic potential and effectiveness on our brain. 'mGluR5' protein having 'PDB ID - 6FFH' was downloaded from RCSB-PDB. Its '.cif' format was converted into '.pdb' format. Similarly, '.sdf' format files of ligands were converted into '.pdb' format using 'CACTUS Online SMILES Translator'. 'mGluR5' having 'pdb' format was opened on 'Discovery Studio' and was cleaned to get prepared for docking. Then, for our reference/standard, 'Fenobam' and 'Minocycline', which have been found to bind to and show efficacy against 'mGluR5' were analysed against 'mGluR5' using 'CB-Dock'. Their docking results were used as reference/standard in this result, with which, docking results of 19 collected phytochemicals were compared. 19 phytochemicals were also docked against 'mGluR5' and their docking results were compared to our references/standards. 'Platainoside B', 'beta-Bisabolene', 'Cirsilineol' and 'Orientin' gave the minimum vina score in the same cavity size, in which, 'Fenobam' gave the minimum vina score, and, were found to be equivalent to 'Fenobam' at the in-silico docking level. Therefore, only these 4 ligands were shortlisted for further research, and, Lipinski's rule of 5 and Absorption, Distribution, Metabolism, Excretion and Toxicity of only these 4 phytochemicals were analyzed using

pkCSM tool. 'Platainoside-B' and 'Orientin' showed violation from Lipinski's rule of 5, in terms of donor and acceptor hydrogen bonds. 'beta-Bisabolene' also showed slight violation in terms of 'logP'.

5. Conclusion

The docking results of 'Platainoside B', 'beta-Bisabolene', 'Cirsilineol' and 'Orientin', nearly resembled the docking result of 'Fenobam'. This indicated that, these four compounds may be the partially validated potential therapeutic molecules against 'mGluR5' like 'Fenobam'. However, analysis of Lipinski's rule of 5 showed that, 'Platainoside-B' and 'Orientin' violated from Lipinski's rule of 5, in terms of donor and acceptor hydrogen bonds. These facts somewhat show that, 'beta-Bisabolene' and 'Cirsilineol' have relatively more probability to serve as therapeutic compounds against 'mGluR5', as compared to 'Platainoside-B', 'Orientin' and other phytochemicals in the list. However, this conclusion is solely drawn from 'in-silico' research. Different results may or may not be observed in 'in-vitro' or 'in-vivo' researches.

6. Future Prospect

This research maybe utilized for further attempt to discover novel therapeutics against 'mGluR5', to treat 'Intellectual disability', in 'Fragile X syndrome'.

REFERENCES

[1] Colom R, Karama S, Jung RE, Haier RJ. Human intelligence and brain networks. Dialogues Clin Neurosci. 2010; 12(4):489-501. doi: 10.31887/DCNS.2010.12.4/rcolom. PMID: 21319494; PMCID: PMC3181994.

[2] Jung RE, Haier RJ. The parieto-frontal integration theory (P-FIT) of intelligence: Converging neuroimaging evidence. Behav Brain Sci. 2007; 30:135-187. doi: 10.1017/S0140525X07001185.

[3] Gray J, Thompson PM. Neurobiology of intelligence: Science and ethics. Nat Rev. 2004; 5:471-482. doi: 10.1038/nrn1405.

[4] Gray J, Chabris C, Braver T. Neural mechanisms of general fluid intelligence. Nat Neurosci. 2003; 6:316-322. doi: 10.1038/nn1014.

[5] Matzel LD, Kolata S. Selective attention, working memory, and animal intelligence. Neurosci Biobehav Rev. 2010; 34:23-30. doi: 10.1016/j.neubiorev.2009.07.002.

[6] Lee K, Cascella M, Marwaha R. Intellectual Disability. [Updated 2023 Jun 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547654/

[7] Jacquemont S, Berry-Kravis E, Hagerman R, et al. The challenges of clinical trials in fragile X syndrome. Psychopharmacology (Berl). 2014 Mar; 231(6):1237-50.

[8] Segawa M. Early motor disturbances in Rett syndrome and its pathophysiological importance. Brain Dev. 2005 Nov; 27 Suppl 1:S54-S58.

[9] Deltour L, Ang HL, Duester G. Ethanol inhibition of retinoic acid synthesis as a potential mechanism for fetal alcohol syndrome. FASEB J. 1996 Jul; 10(9):1050-7.

[10] Biellik RJ, Orenstein WA. Strengthening routine immunization through measles-rubella elimination. Vaccine. 2018 Sep 05; 36(37):5645-5650.

[11] Mitchell CD. HIV-1 encephalopathy among perinatally infected children: Neuropathogenesis and response to highly active antiretroviral therapy. Ment Health Dev Disabil Res Rev. 2006; 12(1):10-22.

[12] Li M, et al. The Association of Maternal Obesity and Diabetes With Autism and Other Developmental Disabilities. Pediatrics. 2016 Feb; 137(2):e20152206.

[13] Huang J, Zhu T, Qu Y, Mu D. Prenatal, Perinatal and Neonatal Risk Factors for Intellectual Disability: A Systemic Review and Meta-Analysis. PLoS One. 2016; 11(4):e0153655.

[14] Camfield PR, Bahi-Buisson N, Trinka E. Transition issues for children with diffuse cortical malformations, multifocal postnatal lesions, (infectious and traumatic) and Lennox-Gastaut and similar syndromes. Epilepsia. 2014 Aug; 55 Suppl 3:24-8.

[15] Picker JD, Walsh CA. New innovations: therapeutic opportunities for intellectual disabilities. Ann Neurol. 2013 Sep; 74(3):382-90. doi: 10.1002/ana.24002. PMID: 24038210; PMCID: PMC3876407.

[16] Ebert DH, Greenberg ME. Activity-dependent neuronal signalling and autism spectrum disorder. Nature. 2013; 493:327-337. doi: 10.1038/nature11860.

[17] Berry-Kravis E, Hessl D, Coffey S, et al. A pilot open label, single dose trial of fenobam in adults with fragile X syndrome. J Med Genet. 2009; 46:266-271. doi: 10.1136/jmg.2008.063701.

[18] Leigh MJ, et al. A randomized double blind, placebo controlled trial of minocycline in children and adolescents with fragile X syndrome. J Dev Behav Pediatr. 2013; 34:147-155. doi: 10.1097/DBP.0b013e318287cd17.

[19] Siller SS, Broadie K. Matrix metalloproteinases and minocycline: therapeutic avenues for fragile X syndrome. Neural Plast. 2012; 2012:124548. doi: 10.1155/2012/124548.

[20] Shisode RN. Herbs for brain disorder. Journal of Preventive Medicine and Holistic Health. 2017; 3(1):1-5. doi: 10.18231/2454-6712.2017.0001.

[21] Gosciniak A, et al. Bacopa monnieri: Preclinical and Clinical Evidence of Neuroactive Effects, Safety of Use and the Search for Improved Bioavailability. Nutrients. 2025; 17(11):1939. https://doi.org/10.3390/nu17111939.

[22] Mikulska P, et al. Ashwagandha (Withania somnifera)-Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics. 2023 Mar 24; 15(4):1057. doi: 10.3390/pharmaceutics15041057.

[23] Singh N, et al. An overview on Ashwagandha: A Rasayana (rejuvenator) of Ayurveda. Afr J Tradit Complement Altern Med. 2011; 8:208-213. doi: 10.4314/ajtcam.v8i5S.9.

[24] Matthews DG, et al. Centella Asiatica Improves Memory and Promotes Antioxidative Signaling in 5XFAD Mice. Antioxidants (Basel). 2019 Dec 8; 8(12):630. doi: 10.3390/antiox8120630.

[25] Gray NE, et al. Centella asiatica increases hippocampal synaptic density and improves memory and executive function in aged mice. Brain Behav. 2018; 8(7):e01024. doi: 10.1002/brb3.1024.

[26] Xu MF, et al. Asiatic acid, a pentacyclic triterpene in Centella asiatica, attenuates glutamate-induced cognitive deficits in mice and apoptosis in SH-SY5Y cells. Acta Pharmacol Sin. 2012; 33:578-587. doi: 10.1038/aps.2012.3.

[27] Kumar A, Prakash A, Dogra S. Centella asiatica Attenuates D-Galactose-Induced Cognitive Impairment, Oxidative and Mitochondrial Dysfunction in Mice. Int J Alzheimers Dis. 2011; 2011:347569. doi: 10.4061/2011/347569.

[28] Wattanathorn J, et al. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of Centella asiatica. J Ethnopharmacol. 2008; 116(2):325. doi: 10.1016/j.jep.2007.11.38.

[29] Bradwejn J, et al. A double-blind, placebo-controlled study on the effects of Gotu Kola (Centella asiatica) on acoustic startle response in healthy subjects. J Clin Psychopharmacol. 2000; 20:680-684. doi: 10.1097/00004714-200012000-00015.

[30] Soumyanath A, et al. Centella asiatica accelerates nerve regeneration upon oral administration and contains multiple active fractions increasing neurite elongation in-vitro. J Pharm Pharmacol. 2005; 57:1221-1229. doi: 10.1211/jpp.57.9.0018.

[31] Rather MA, et al. Neuroprotective role of Asiatic acid in aluminium chloride induced rat model of Alzheimer's disease. Front Biosci (Schol Ed). 2018; 10:262-275. doi: 10.2741/s514.

[32] Kumar A, Dogra S, Prakash A. Neuroprotective Effects of Centella asiatica against Intracerebroventricular Colchicine-Induced Cognitive Impairment and Oxidative Stress. Int J Alzheimers Dis. 2009; 2009:972178. doi: 10.4061/2009/972178.

[33] Kumar MHV, Gupta YK. Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. Clin Exp Pharmacol Physiol. 2003; 30:336-342. doi: 10.1046/j.1440-1681.2003.03842.x.

[34] Kumar MHV, Gupta YK. Effect of different extracts of Centella asiatica on cognition and markers of oxidative stress in rats. J Ethnopharmacol. 2002; 79:253-260. doi: 10.1016/S0378-8741(01)00394-4.

[35] Prakash A, Kumar A. Mitoprotective effect of Centella asiatica against aluminum-induced neurotoxicity in rats: Possible relevance to its antioxidant and anti-apoptosis mechanism. Neurol Sci. 2013; 34:1403-1409. doi: 10.1007/s10072-012-1252-1.

[36] Pattanayak P, et al. Ocimum sanctum Linn. A reservoir plant for therapeutic applications: An overview. Pharmacogn Rev. 2010 Jan; 4(7):95-105. doi: 10.4103/0973-7847.65323.

[37] C M MG, et al. Ocimum tenuiflorum extract (HOLIXER): Possible effects on hypothalamic-pituitary-adrenal (HPA) axis in modulating stress. PLoS One. 2023 May 4; 18(5):e0285012. doi: 10.1371/journal.pone.0285012.

[38] Vivek-Ananth RP, et al. IMPPAT 2.0: An Enhanced and Expanded Phytochemical Atlas of Indian Medicinal Plants. ACS Omega. 2023; 8(9):885. doi: 10.1021/acsomega.3c00156.

[39] Burley SK, et al. Updated resources for exploring experimentally-determined PDB structures and Computed Structure Models at the RCSB Protein Data Bank. Nucleic Acids Res. 2025; 53(D1):D564-D574. https://doi.org/10.1093/nar/gkae1091.

[40] Berman HM, et al. How community has shaped the Protein Data Bank. Structure. 2013; 21(9):1485-1491. doi: 10.1016/j.str.2013.07.010.

[41] Zardecki C, et al. RCSB Protein Data Bank: A Resource for Chemical, Biochemical, and Structural Explorations of Large and Small Biomolecules. J Chem Educ. 2016; 93(3):569-575. doi: 10.1021/acs.jchemed.5b00404.

[42] Kim S, et al. PubChem Substance and Compound databases. Nucleic Acids Res. 2016; 44(D1):D1202-D1213. https://doi.org/10.1093/nar/gkv951.

[43] CACTUS Online SMILES Translator. Available from: https://cactus.nci.nih.gov/translate/

[44] Liu Y, et al. CB-Dock: a web server for cavity detection-guided protein-ligand blind docking. Acta Pharmacol Sin. 2020; 41:138-144. https://doi.org/10.1038/s41401-019-0228-6.

[45] Pires DEV, et al. pkCSM: predicting small-molecule pharmacokinetic properties using graph-based signatures. J Med Chem. 2015; 58(9):4066-4072.

[46] Roskoski R. Properties of FDA-approved small molecule protein kinase inhibitors. Pharmacol Res. 2019; 144:19-50. doi: 10.1016/j.phrs.2019.03.006.

[47] RCSB PDB Structure 6FFH. doi: 10.2210/pdb6FFH/pdb.

[48] IMPPAT Phytochemical: Ocimum tenuiflorum. https://cb.imsc.res.in/imppat/phytochemical/Ocimum%20tenuiflorum

[49] IMPPAT Phytochemical: Centella asiatica. https://cb.imsc.res.in/imppat/phytochemical/Centella%20asiatica

[50] IMPPAT Phytochemical: Bacopa monnieri. https://cb.imsc.res.in/imppat/phytochemical/Bacopa%20monnieri

[51] IMPPAT Phytochemical: Withania somnifera. https://cb.imsc.res.in/imppat/phytochemical/Withania%20somnifera

[52] IMPPAT Database. https://cb.imsc.res.in/imppat/

[53] CB-Dock. http://clab.labshare.cn/cb-dock/

[54] pkCSM. https://biosig.lab.uq.edu.au/pkcsm/