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Evaluation of Bioactive Compounds Obtained from Ginkgo Biloba Against Crystal Structure of Myelin Oligodendrocyte Glycoprotein (MOG)

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Abstract

Multiple Sclerosis (MS) spreads rapidly across the globe, causing almost 2.8 million cases worldwide. Many drugs and inhibitors, such as dronabinol and nabilone, have been used to treat MS, but there is no effective treatment for MS till now as these medications can cause severe side effects. So, we tested different compounds from *Ginkgo biloba* to inhibit the symptoms caused by MS as an herbal treatment. We targeted the Crystal structure of Myelin Oligodendrocyte Glycoprotein as it has shown some excellent results in experimental labs. In

this article, the binding interactions through the molecular docking model was performed. Further compound's effectiveness through various screening protocols such as the ADME Test, Bioavailability Radar Test, and BOILED-Egg Test has been done. This study found that Amentoflavone and Isoginkgetin have the potential to inhibit the Crystal Structure of Myelin Oligodendrocyte Glycoprotein as they show the least binding energies which are -7.79 kcal/mol and -8.14 kcal/mol. To check the effectiveness of these compounds, Molecular Dynamics Simulations and in-vitro studies can be done to find some possible herbal treatments for Multiple Sclerosis.

Keywords
Multiple sclerosis; *Ginkgo biloba*; bioactive compounds; molecular docking; Myelin Oligodendrocyte Glycoprotein (MOG)

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder that affects the central nervous system (CNS), which includes the brain and spinal cord [1]. MS causes damage to the myelin sheath, the protective covering surrounding nerve fibers, which disrupts the communication between the brain and other parts of the body. This leads to various symptoms that can vary in severity and duration, depending on the location and extent of the damage [2]. This inflammation can cause damage to the nerve fibers and disrupt the signals they send to the brain [3]. As the inflammation persists, it can cause further damage to the myelin sheath and lead to the formation of scar tissue or sclerosis, which can further disrupt the communication between nerves [4]. The myelin sheath is essential for efficiently transmitting nerve impulses, and when it's damaged, nerve signals can slow down or become blocked entirely [5]. This results in various symptoms, such as numbness, weakness, tingling, and vision problems [6]. The inflammation and demyelination caused by MS can result in the formation of lesions, or areas of damage, on the CNS [7]. These lesions can occur anywhere in the brain, spinal cord, or optic nerves varying in size and severity [8].

Herbal plants have been studied for their potential role in treating MS. There are many ways in which herbal extracts can be used in treating Multiple sclerosis, such as their anti-inflammatory effects. Since inflammation is a significant contributor to the damage in the CNS in MS, these extracts may help reduce inflammation and prevent further damage [9]. Other benefits include antioxidant, immune-modulating, and neuroprotective effects [10]. Herbal plants such as *Ginkgo biloba* have antioxidant effects that may help to protect against oxidative damage and reduce the severity of MS symptoms [11]. *Ginkgo biloba* have shown neuroprotective effects, which may help to protect the nerve cells in the CNS from damage and improve the symptoms of MS [11]. According to several studies, *Ginkgo biloba* can enhance memory, attention, and thinking speed in healthy adults and people experiencing age-related cognitive decline [12-14].

Computational biology is a field of biology that uses computer-based techniques to analyze and interpret biological data. It is an essential tool in molecular docking, as it allows researchers to predict how a small molecule will interact with a target protein based on its chemical and structural properties [15]. Molecular docking is a computational technique to predict the binding of small

molecules, such as drugs or natural compounds, to a target protein. It is an essential tool in drug discovery and development, as it allows researchers to identify potential drug candidates that may have therapeutic effects in treating various diseases, including multiple sclerosis [16]. Molecular docking and computational biology can predict the binding affinity of a small molecule to a target protein, which measures of how tightly the two molecules will bind to each other. This information is critical in identifying potential drug candidates that may have therapeutic effects in treating MS [17].

2. Materials and Methods

2.1 Ligand Selection

Ginkgo biloba, known for its uses in healthcare was selected for this study. Several research papers were studied to get the data about bioactive compounds of *Ginkgo biloba.* A total of 15 bioactive compounds were used for this study. These bioactive compounds were taken from *Ginkgo biloba* [18, 19]. The compounds which were extracted from this plant were used in molecular docking. The structures were downloaded in .sdf format from PubChem databank, but docking is only possible in .pdb format, so all the extensions were changed to .pdb files using PyMol software [20].

2.2 Receptor

The receptor was Myelin Oligodendrocyte Glycoprotein, a glycoprotein crystal structure. The RCSB PDB data archive was used to obtain the 3D structure of MS in PDB format [21].

Myelin oligodendrocyte glycoprotein (MOG) is a protein found in the central nervous system (CNS), specifically in the myelin sheath surrounding nerve fibers. It plays a role in maintaining the integrity of the myelin sheath, which is essential for proper nerve signal transmission. Oligodendrocytes use the MOG receptor to interact with the myelin sheath. If the receptor is dysfunctional, oligodendrocytes may have difficulty producing and maintaining myelin. This can lead to insufficient myelination of nerve fibers, resulting in slower nerve signal transmission. Dysfunctional MOG receptors can contribute to the breakdown of existing myelin sheaths. Demyelination is a hallmark of several neurodegenerative diseases, such as multiple sclerosis (MS). When myelin is damaged or destroyed, it can disrupt nerve signal conduction and lead to various neurological symptoms, including weakness, numbness, and problems with coordination.In some cases, dysfunction of MOG receptors may trigger an autoimmune response. The immune system may mistakenly target the MOG protein, leading to inflammation and damage to myelin in the CNS. This autoimmune response is associated with demyelinating diseases, such as MOG antibody-associated encephalomyelitis (MOG-EM), which can cause neurological symptoms [22].

2.3 ADME Analysis Test

The initial screening of ligands was conducted using a web-based program named SwissADME. Molecular weight should not be greater than500 Da, high lipophilicity, Log P less than 5, hydrogen bond donors should be less than 5, and hydrogen acceptors should be less than 10 are the five factors examined by this test. Ligand violation denotes that the drug is unfit for production, which is carried out following Lipinski's regulation [23].

ADME analysis, which stands for Absorption, Distribution, Metabolism, and Excretion, is a crucial process in drug development and screening [24]. It helps to evaluate how a substance, such as a cannabinoid, is absorbed, distributed, metabolized, and eliminated by the body. By understanding the ADME properties of cannabinoids, we gained insights into their pharmacokinetics and potential therapeutic use [25].

2.4 Molecular Docking

For obtaining protein-ligand complexes, use Autodock 4.2. Before molecular docking, the autoantigen underwent processing and optimization. The removal of inhibitor molecules was done distantly by the receptor first. Polar hydrogens, Kollman charges, and Gasteiger charges were included in this study. To ensure that the ligand binding position is not restricted to a particular region, the protein molecule was engulfed within a grid box [26]. Following the docking procedure, a DLG file is produced in which the binding energies of various docking locations are determined in a total of 20 conformations in each ligand. The ligand shape with the lowest binding point was chosen [27].

2.5 Bioavailability Radar

The SwissADME tool is used to analyze the drug likelihood of different cannabinoids with binding energies lower than the control, after which six properties are taken into consideration to create a bioavailability radar. The six factors we consider are solubility, size, lipophilicity, polarity, flexibility, and saturation. The pink-shaded area indicates the optimal values of the six parameters, and any deviation from these regions suggests that the ligand should not be orally bioavailable [28]. It provides a graphical representation of the predicted bioavailability profile of a compound based on its physicochemical properties. The Bioavailability Radar enables researchers to assess a compound's drug-likeness and potential oral absorption [29].

2.6 BOILED-Egg

At various stages of drug discovery, gastrointestinal adsorption and brain access are two pharmacokinetic behaviors of critical significance. Calculating the polarity and lipophilicity of small molecules is how the BOILED-Egg, also known as the Brain or IntestinaL Estimated Permeation Method, functions as an accurate predictive model. Physical-chemical descriptors are used to derive predictions of both gut and brain penetration, which are then converted into molecular designs created by models that are quick to run, conceptually simple, and accurate.

BOILED-Eggs contain molecules called "dots" in the yolk that are thought to passively penetrate the blood-brain barrier. The molecules in BOILED-Egg white's "dots" are expected to permeate the digestive system passively. The CNS is expected to bind to the molecules in blue dots via P-glycoprotein. Red dots indicate molecules for which P-glycoprotein association with the CNS is not likely [30].

3. Results

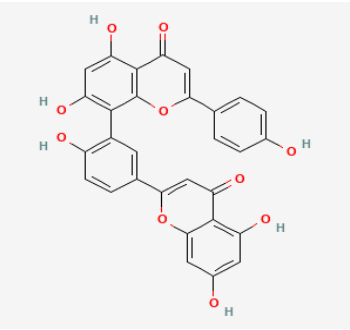
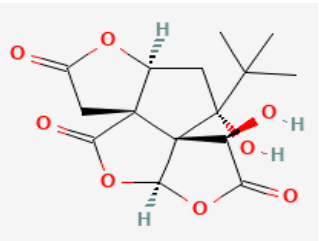
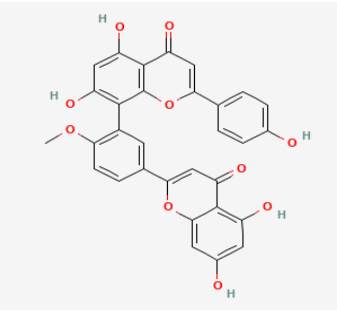
3.1 ADME Analysis Test

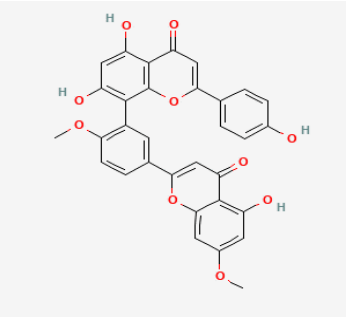
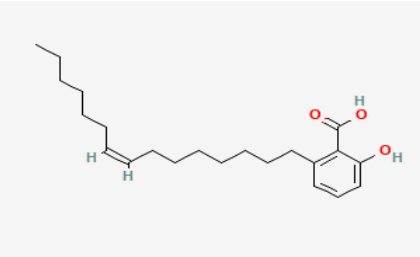
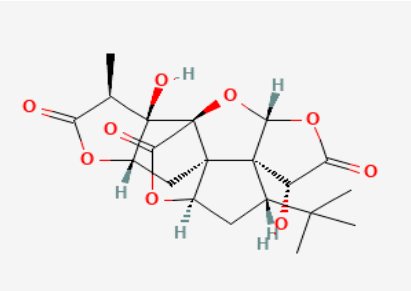
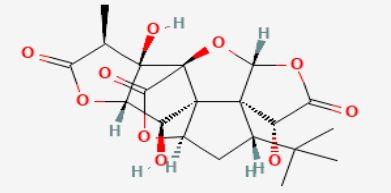
The 15 bioactive components of *Ginkgo biloba* were subjected to Lipinski's law of five. Using physiochemical differences, we can remove substances using this technique. All bioactive compounds in *Ginkgo biloba* revealed 0 to 3 violations, and all ligands were subjected to molecular docking. Compounds that violated the Lipinski rule were also taken. All of the bioactive compounds were examined using the following 5 criteria, which are enumerated below:

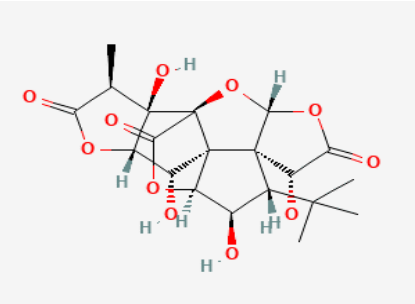
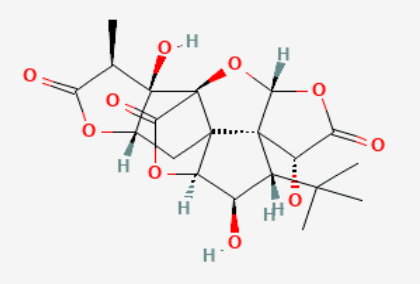
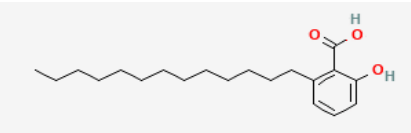
1. Molecular weight (<500 Da) as Measure 1
2. Lipophilicity (LogP < 5) as Measure 2
3. H bond donor (<5) as Measure 3
4. H bond acceptor (<10) as Measure 4
5. Violations as Measure 5

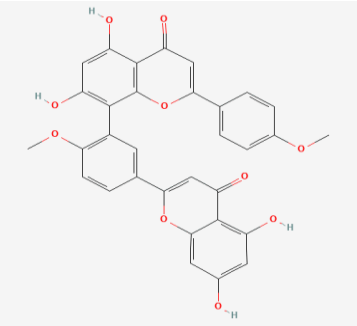
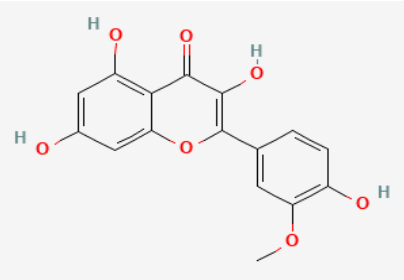
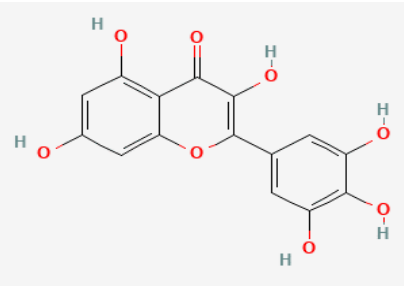
So, all these parameters of the specific compound are listed below in Table 1 with the values of all the parameters:

Table 1 ADME Analysis table of 15 bioactive compounds from *Ginkgo biloba.*

Compound Name	Structure	PubChem ID	Analysis Parameter	
Amentoflavone		5281600	Measure 1	538.46 g/mol
			Measure 2	5.04
			Measure 3	6
			Measure 4	10
			Measure 5	2
Bilobalide		73581	Measure 1	326.30 g/mol
			Measure 2	-0.27
			Measure 3	2
			Measure 4	8
			Measure 5	0
Bilobetin		5315459	Measure 1	522.48 g/mol
			Measure 2	5.36
			Measure 3	5
			Measure 4	10
			Measure 5	1

Ginkgetin		5271805	Measure 1	566.51 g/mol
			Measure 2	5.69
			Measure 3	4
			Measure 4	10
			Measure 5	1
Ginkgolic acid		5281858	Measure 1	346.50 g/mol
			Measure 2	8.55
			Measure 3	2
			Measure 4	3
			Measure 5	1
Ginkgolide A		9909368	Measure 1	408.40 g/mol
			Measure 2	0.59
			Measure 3	2
			Measure 4	9
			Measure 5	0
Ginkgolide B		6324617	Measure 1	424.40 g/mol
			Measure 2	-0.38
			Measure 3	3

			Measure 4	10
			Measure 5	0
Ginkgolide C		24721502	Measure 1	440.40 g/mol
			Measure 2	-1.36
			Measure 3	4
			Measure 4	11
			Measure 5	1
Ginkgolide J		24721483	Measure 1	424.40 g/mol
			Measure 2	-0.38
			Measure 3	3
			Measure 4	10
			Measure 5	0
Ginkgoneolic acid		161306	Measure 1	320.47 g/mol
			Measure 2	8.18
			Measure 3	2
			Measure 4	3
			Measure 5	1
Isoginkgetin		5318569	Measure 1	566.51 g/mol

			Measure 2	5.69
			Measure 3	4
			Measure 4	10
			Measure 5	1
Isorhamnetin		5281654	Measure 1	316.26 g/mol
			Measure 2	1.87
			Measure 3	4
			Measure 4	7
			Measure 5	0
Myricetin		5281672	Measure 1	318.24 g/mol
			Measure 2	1.18
			Measure 3	6
			Measure 4	8
			Measure 5	1
Sciadopitysin		5281696	Measure 1	580.54 g/mol
			Measure 2	6.02
			Measure 3	3

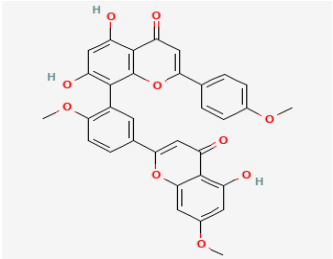
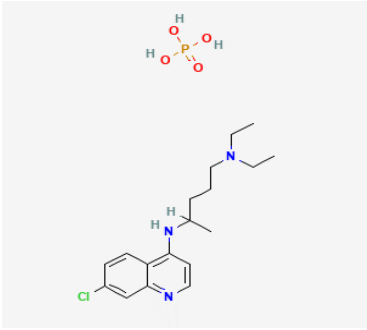
			Measure 4	10
			Measure 5	1
Tanakan		2719	Measure 1	417.87 g/mol
			Measure 2	0.26
			Measure 3	4
			Measure 4	6
			Measure 5	0

Table 1 includes all the parameters that involve the ADME analysis test and helps in eliminating the compounds that violate the rules.

3.2 Molecular Docking

15 bioactive compounds obtained from *Ginkgo biloba* are subjected to the docking process (Table 2). Molecular docking is one of the power takes of bioinformatics. This tool is beneficial in visualizing the docking of ligands to proteins; thus, a complex of ligands and proteins is formed and gives us the binding energy values and all the binding energy values have been mentioned in Table 2. All the data that we obtain through the process of docking is used for drug discovery. Isoginkgetin, which is one of the bioactive molecules, had the lowest binding energy value of all of them at -8.14 kcal/mol, followed by Amentoflavone, which had a binding energy value of -7.79 kcal/mol.

Table 2 Results of molecular docking of 15 ligands from *Ginkgo biloba* against MOG receptor using Autodock 4.2.

S. No.	Ligands	Binding Energy (ΔG) (kcal/mol)	Ligand Efficiency	Inhibition Constant (μM)	Intermolecular Energy (kcal/mol)	Vdw H-bond desolvation (kcal/mol)
1	Amentoflavone	-7.79	-0.19	1.97	-10.47	-9.38
2	Bilobalide	-5.2	-0.23	153.17	-6.1	-5.88
3	Bilobetin	-7.56	-0.18	2.87	-10.25	-9.51
4	Ginkgetin	-7.24	-0.17	4.9	-9.93	-9.58
5	Ginkgolic acid	-7.02	-0.28	7.2	-11.79	-6.11
6	Ginkgolide A	-5.84	-0.2	52.82	-6.73	-6.6
7	Ginkgolide B	-5.93	-0.2	45.16	-7.12	-6.62
8	Ginkgolide C	-6.13	-0.2	31.85	-7.63	-7.07
9	Ginkgolide J	-5.87	-0.2	49.66	-7.06	-6.89
10	Ginkgoneolic acid	-7.04	-0.31	6.94	-11.51	-7.21
11	Isoginkgetin	-8.14	-0.19	1.08	-10.83	-9.94
12	Isorhamnetin	-5.52	-0.24	90.34	-7.31	-6.88
13	Myricetin	-5.37	-0.23	116.79	-7.45	-6.95
14	Sciadopitysin	-7.67	-0.18	2.4	-10.35	-10.06
15	Tanakan	-5.04	-0.23	202.15	-7.43	-6.58

Table 2 consists of all the binding energies that we obtained after docking the crystal structure of MOG and the various bioactive compounds as listed in the table.

3.3 Interactions

They were showing 2D interactions of the various compounds with the MOG with the help of Discovery Studio. BIOVIA Discovery Studio is a comprehensive computational chemistry and molecular modelling software. It offers various tools for studying 2D interactions between

molecules. The software enables the visualization of chemical structures in a 2D representation, allowing researchers to analyze the arrangement of atoms and structural features. Additionally, it facilitates molecular docking, which predicts the binding interactions between small molecules and target proteins [31]. Users can assess and visualize different types of 2D interactions, such as hydrogen bonds and hydrophobic interactions, to understand the nature and strength of ligand-receptor interactions. The software also supports pharmacophore modelling, scaffold hopping, similarity searching, and virtual screening, aiding in the exploration of chemical space and identifying molecules with desired interaction profiles. Overall, BIOVIA Discovery Studio is a valuable tool for analyzing and predicting 2D interactions between molecules, contributing to drug discovery and molecular design efforts [32].

Figure 1 and Figure 2 shows the 2D interactions between the Amentoflavone and Isoginkgetin with the crystal structure of Myelin Oligodendrocyte Glycoprotein.

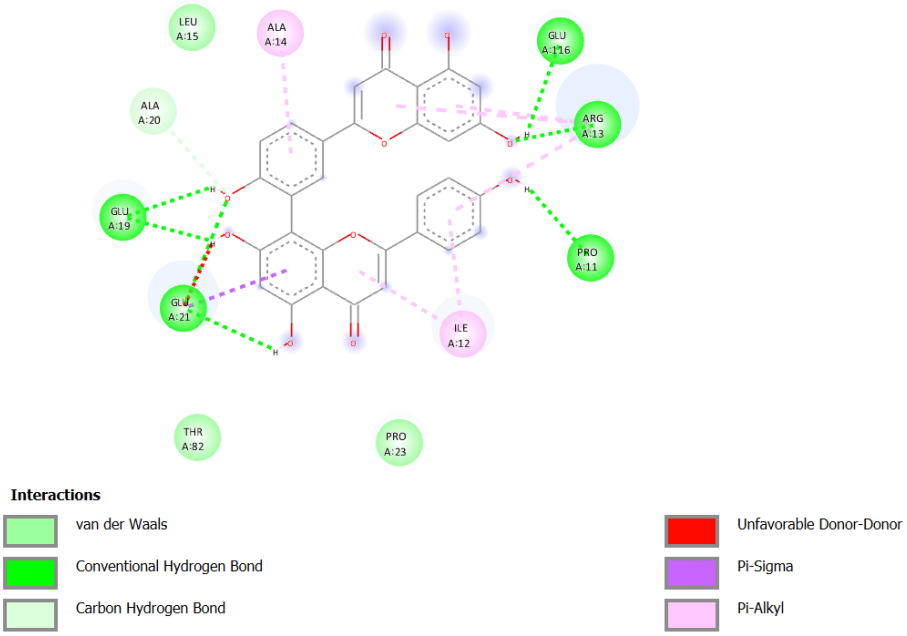


Figure 1 Interaction between Amentoflavone and MOG.

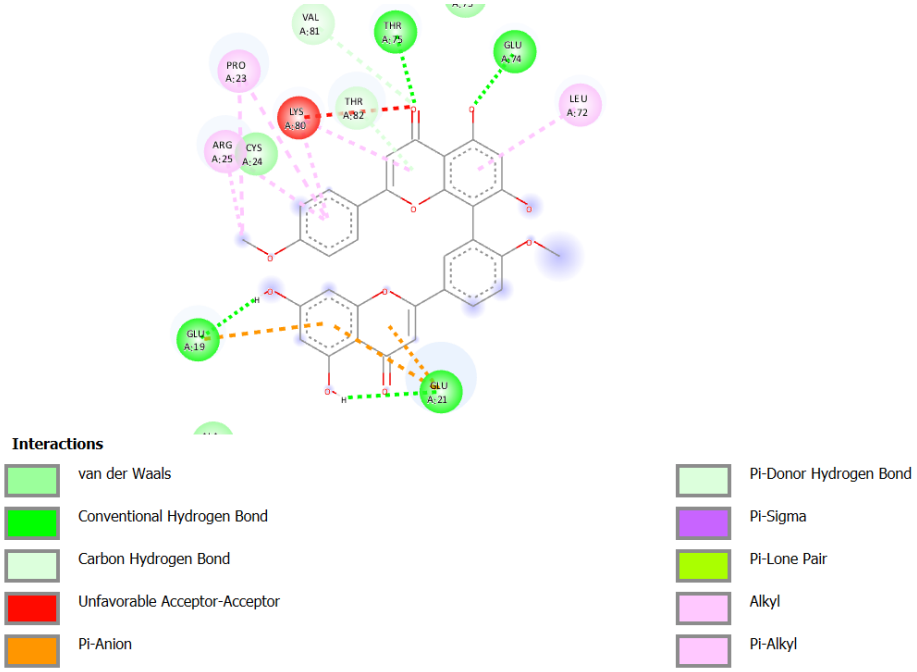


Figure 2 Interaction between Isoginkgetin and MOG.

Figure 1 shows that among the 20 conformations of Amentoflavone, -7.79 was the measured least binding energy. Six various forms of contact were noticed, including van der Waals, Conventional hydrogen bond, Pi-alkyl, Pi-sigma, and Carbon hydrogen bond, and an unfavorable donor-donor. The ligand has interacted with the ALA:14, GLU:116, ARG:13, PRO:11, ILE:12, GLU:21, GLU:19, and ALA:20 of the crystal structure of MOG.

Figure 2 shows that among the 20 conformations of Isoginkgetin, -8.14 was the measured least binding energy. Ten various forms of contact were noticed, including van der Waals, Conventional hydrogen bond, alkyl, Pi-Alkyl, Pi-lone pair, Pi-sigma, Pi-Anion, Pi-Donor Hydrogen bond, and Carbon hydrogen bond, and an unfavorable acceptor-acceptor**.** The ligand has interacted with the GLU:21, GLU:74, THR:75, LEU:72, THR:82, LYS:80, VAL:81, ARG:25, PRO:23, CYS:24 and GLU:19 of the crystal structure of MOG.

3.4 Bioavailability Radar

Furthermore, the analysis includes ligands, and a study was done using bioavailability radar. It is used to look into the ligands'' drug likeliness, which is established on 6 properties. Studies showed that some ligands were orally available as some fitted the radar's pink-shaded region. So, some of the selected ligands are orally bioavailable, and some should be given in some other form. We have selected only two compounds for this study as only these two compounds showed promising results in the molecular docking studies.

Figure 3 and Figure 4 show that the pink-shaded zone is an estimated physicochemical space for oral bioavailability. LIPO (Lipophility): -0.7 < XLOGP3 < + 5.0. SIZE: 150 g/mol < MV < 500 g/mol. POLAR (Polarity: 0 < LogS (ESOL) < 6. INSATU (Insaturation): 0.25 < fraction Csp3 < 1. FLEX (Flexibility): 0 < Number of rotatable bonds < 9): 20Å^2 < TPSA < 130Å^2. INSOLU (Insolubility)

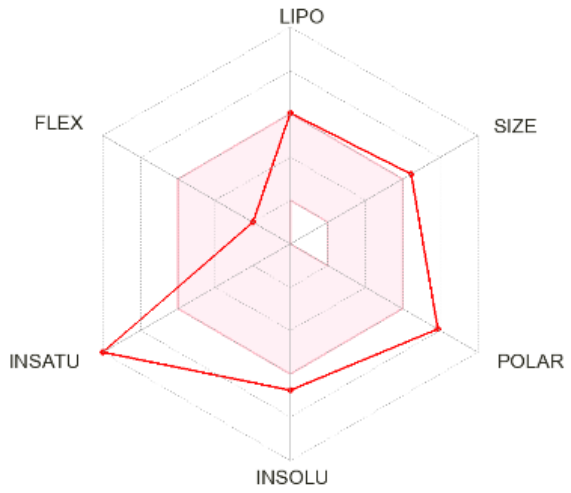


Figure 3 Bioavailability Radar of Amentoflavone.

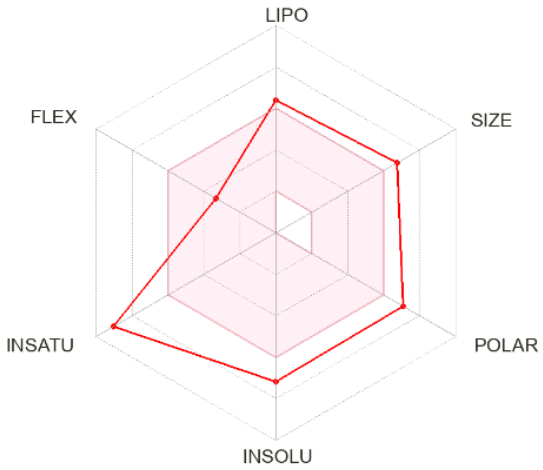


Figure 4 Bioavailability Radar of Isoginkgetin.

Figure 3 shows that Amentoflavone doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.

Figure 4 shows that Isoginkgetin doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.

3.5 BOILED-Eggs

BOILED-Egg was checked for all the 15 bioactive compounds, and it showed some alarming results as all the molecules were not able to cross the Blood Brain Barrier, and many of them were out of range, but some were also able to cross the gastrointestinal tract. We can say this by seeing the BOILED-Eggs as the molecules present within the white portion and some in the yellow part. We have selected only two compounds for this study as only these compounds showed promising results in the molecular docking studies.

Figure 5 and Figure 6 shows BOILED-Eggs of two bioactive compounds. Molecules in the yellow portion show that they can cross BBB, and molecules in the white region showed that molecules can cross the gastrointestinal tract, and molecules present outside are out of range.

Figure 5 BOILED-Egg of Amentoflavone.

Figure 6 BOILED-Egg of Isoginkgetin.

Figure 5 shows that the Molecule is out of range, and glycoprotein association with CNS is not expected.

Figure 6 shows that the Molecule is out of range, and glycoprotein association with CNS is not expected.

4. Discussion

In this study, 15 bioactive compounds were obtained from *Ginkgo biloba.* The compounds were first downloaded and screened using Lipinski's rule of five and the ADME Analysis Test to examine the compound's drug probability and eliminate those compounds that violate the rules and remove them from our study. No compound violates the rule so we took all the compounds in the docking process. All of the compounds were drug-friendly and subsequently underwent molecular docking. We then analyzed the docking results using Autodock 4.2 and found that Isoginkgetin and Amentoflavone were the most useful in binding energy. All the compounds showed some good results, so process further for bioavailability radar studies.

All the ligands were then run on the bioavailability radar, and some of them fitted in the pink-shaded region, which means those compounds are orally bioavailable. Many did not fit in the region so they have to be processed for industrial use as they are not orally bioavailable. BOILED-Egg was used to study whether the compound will cross the BBB. This study showed that only some

compounds can cross BBB, and many combinations were out of range too, which concludes that *Ginkgo biloba* is not a very great choice to treat neurological disorders, but it can be used in industry to process further as it has a good affinity with Myelin Oligodendrocyte Receptor.

By studying all the data obtained through different studies it was clearly observed that those two compounds, Amentoflavone and Isoginkgetin, are the potential leads. By processing these substances and finding the valuable part in this compound, can make them orally bioavailable so that these compounds can confirm that they can repress the symptoms. As most of the compounds will not cross BBB, their properties can be enhanced by performing various experiments on their structure so that they can be given directly to the patients. The major benefit of using these compounds is that they aren't toxic and there are no signs of causing some severe side effects in the body. These compounds can be our best shot for future studies if we look to work with Ginkgo biloba as our target for herbal therapy.

Industries has developed the techniques to change the naturally occurring compounds so that they can be absorbed in the body efficiently. So, the compounds that strongly interact with the MOG can be innovated and used for the therapeutic purpose of decreasing the symptoms caused by the demyelination of neurons.

5. Conclusions

Multiple sclerosis is a complex and multifaceted disease, and its treatment typically involves a combination of approaches, including disease-modifying therapies, symptom management, and lifestyle interventions, and more research on Multiple Sclerosis remains ongoing in neuroscience. *Ginkgo biloba* contains several bioactive compounds, such as flavonoids and terpenoids, with antioxidant and anti-inflammatory properties. *Ginkgo biloba* gains a lot of attention because of these properties as they have been tested in animal models and reported positive outcomes. Some studies have reported that it can be used to repress the symptoms caused by demyelination of the neurons because of its cognitive efficiency. To date, few clinical trials have examined the effects of *Ginkgo biloba* in MS patients and found some positive results on attention and processing speed. However, more rigorous clinical trials are needed to draw definitive conclusions about its potential benefits in MS treatment. Due to the lack of facilities to conduct the in-vitro studies for this specific compound, we aim to provide valuable insights into the treatments of Multiple Sclerosis. By using Molecular Docking studies, we can find combinations with a bit of efficiency and save time in future studies. This study concluded that many naturally occurring substances can be excluded from neuroscience studies as they have not shown positive results. This study provides insights into herbal treatment with naturally occurring substances such as Amentoflavone and Isoginkgetin. By performing in-vitro studies in the future, we can see the possible advantages of these compounds or their synthetic derivatives, which can either help or not in treating the symptoms caused by Multiple Sclerosis.

Author Contributions

AR planned the overall content of the paper. AG perform all the experimentation work. AR, AG, wrote the manuscript. SP, Np and SR review the manuscript. All the authors approved the final version.

Competing Interests

The authors have declared that no competing interests exist.

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