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Molecular docking analysis of *Mentha X Piperita* derived ligands for targeting migraine receptors: Identification and evaluation of high-affinity compounds

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This current research is focused on finding ligands of the *Mentha x piperita* plant (peppermint) and investigating the interaction of chosen ligands with the migraine receptors. Until now, the chemical drugs used in the treatment of migraine have had many side effects. Traditionally, compounds from the peppermint plant have been used for lowering migraine attacks in Ayurvedic treatments. Hence, various bioactive compounds are chosen as the ligands for this study, with RAMP, $5HT_{1F}$, and $5HT_{1A}$ receptors chosen because of their role in the modulation of physical and neurological pathways. Molecular docking was done using Auto Dock vina 1.5.7 software, and each ligand was selected for further studies using the binding affinity from the molecular docking. The ligands with the lowest binding score are Eriodictyol for RAMP with a score of -7 (Kcal/mol) and Luteolin, Eriodictyol for $5HT_{1A}$ with a score of -8.6 (Kcal/mol),-8.4 (Kcal/mol) respectively, and Luteolin, Eriodictyol for $5HT_{1F}$ with the score of 8.9 (Kcal/mol),-8.4 (Kcal/mol) respectively. These ligands for the respective receptors satisfied Lipinski's rule and had all drug-like properties. The stability and dynamics of the protein-ligand complex were studied by the simulation software Sibiolead. The results showed that all selected ligands stably interact with the receptors. Therefore, the findings of current research suggest that the selected ligands can be potential drug candidates capable of targeting the migraine receptors.

Keywords: $5HT_{1A}$, $5HT_{1F}$, Eriodictyol, Luteolin, *Mentha piperita*, RAMP, Simulation

Migraine is a common episodic neurological disorder often associated with severe headaches and other related features such as nausea, phonophobia, and photophobia[1]. This disorder is characterised by episodes of head pain that are often throbbing and frequently unilateral and may be severe. Commonly, migraine is classified as Migraine without Aura and Migraine with Aura[2-3]. Migraine with Aura is also known as common migraine, where the attacks are associated with nausea, vomiting, or sensitivity to light, sound, or movement[4]. Without treatment, this will continue to last from 4 to 72 h. The exact mechanism was not completely understood, but it is believed to involve a combination of genetic, environmental, and neurovascular factors[5]. The activation of the trigeminal nerve system and the release of neuropeptides such as CGRP (Calcitonin gene-related peptide) play key roles[6]. Migraine with Aura is also known as classic migraine, which is associated with a similar headache that is seen in migraine without aura but is preceded or accompanied by neurological symptoms known as "Aura"[7]. This lasts from 5 to 60 min and may include visual disturbances (such as flashes of light, Zigzag patterns or blind spots), sensory disturbances, and occasionally speech disturbances. Headaches which is similar to migraine without Aura (throbbing, unilateral, pain). Associated symptoms include nausea and sensitivity to light and sound as seen in migraine without aura[8].

In this current study, RAMP, $5HT_{1F}$, and $5HT_{1A}$ receptors have been selected that are predominantly studied in the research of migraine-related neurological pathways and treatment[9]. These receptors are mainly focused on due to their involvement in the symptoms of migraine, which include vomiting, headache, pain, nausea, etc[10]. The $5HT_{1F}$ receptor is a subtype of serotonin receptors found in the brain. They are implicated in the modulation of pain pathways, including those involved in migraine[11]. Their mechanism of action

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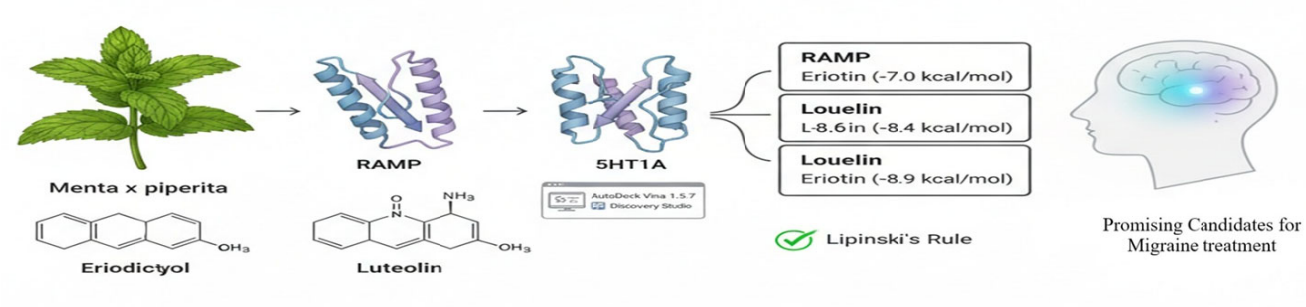

Graphical abstract

involves that drugs targeting $5HT_{1F}$ receptors exert their effects by inhibiting the release of neurotransmitters associated with pain transmission. This mechanism is distinct from other serotonin receptor subtypes targeted in migraine treatment[12]. These drugs aim to provide relief by specifically targeting the pathways involved in migraine without the cardiovascular side effects. The$5HT_{1A}$ receptor is a subtype of serotonin receptor that plays a key role in various neurological processes that including mood regulation and pain modulation[13-14]. During a migraine attack, changes in the availability of these receptors in the brainstem can influence the pathways involved in headache mechanisms. These are inhibitory receptors and, when activated by serotonin (5-HT), can reduce neuronal excitability and modulate pain perception. The mechanism explains that in migraine, fluctuations in serotonin levels can lead to changes in receptor availability. During an attack, there may be a decrease in $5HT_{1A}$ receptor activity, which contributes to the sensitisation of pain pathways[15]. Alterations in $5HT_{1A}$ receptor availability can disrupt normal serotonergic signalling, leading to heightened pain sensitivity and the onset of migraine symptoms. Receptor Activity-Modifying Proteins (RAMPs) are important for the functioning of Class B G Protein-Coupled Receptors (GPCRs), particularly in the context of calcitonin gene-related peptide (CGRP) receptors, which are significant in migraine pathology[16-17]. RAMPs modulate the expression, localisation and signalling of Class B GPCRs. The CGRP receptor, when associated with RAMP1, responds to CGRP binding, activating the intracellular signalling pathway[18]. The mechanism involves elevated CGRP levels during migraines, which contribute to vasodilation and sensitisation of pain pathways. Targeting the CGRP receptor with antagonists can block this signalling, reducing headache frequency and intensity. The development of CGRP receptor antagonists highlights the importance of RAMPs in migraine treatment, which enables targeted modulation of the CGRP signalling pathway[19-22].

Peppermint is a perennial. and a strongly scented herb belonging to the family Lamiaceae. It is cultivated in a temperate region of Europe, Asia, the United States, India, and Mediterranean countries because of its commercial value and distinct aroma[23-24]. *Mentha piperita* is well recognised for treating fever, cold, digestive issues, anti-viral, anti-fungal, oral mucosa, and throat inflammation. The scientific studies describe the use of *Mentha piperita* for biological effects such as anti-oxidant, anti-microbial, anti-viral, anti-inflammatory, bio-pesticidal, larvicidal, anticancer, radioprotective effect, genotoxicity, and anti-diabetic activity[25-26].

Materials and Methods

Preparation of ligand and target protein

The 3D PDB structure of the protein molecule is obtained from the RCSB PDB database, and the 3D PDB structure of ligands has been obtained from the IMPPAT database and the PubChem database. Peppermint-derived ligands were identified through the literature[27-30]. They are changed into PDBQT format using AutodockVina software. For changing the PDB into a PDBQT file, the protein is given in the PDB format to the Autodock Vina interface and the water molecule is deleted, and Kollman charges are added to the protein structure, and only the non-polar molecules have been included, and others have been deleted. The ligand molecules are given in PDB format, and they are changed into PDBQT format using Autodock Vina software.

Study of receptor-ligand interaction using molecular docking

Using AutodockVina, the molecular docking was performed, and the whole protein molecule was

selected by adjusting the grid box, and the parameters of the grid box are noted in a new grid file. Next, the molecular docking was performed by giving the path of the file in which the PBDQT file of the receptor, ligand is stored, and the program is executed, and then the binding affinity is noted, and the receptor-ligand molecule that has the highest binding affinity is selected for further studies[31-32]. The selected receptor-ligand molecule structure has been visualised using the software BIOVIA Discovery Studio, and its respective picture, which also shows the hydrogen donor and hydrogen acceptor, has been visualised, and the 2D interaction picture of the receptor-ligand has been obtained. Also, the number of hydrogen molecules involved in the interaction is noted that are important for the protein-ligand interaction. Various other parameters, such as hydrogen bond donor, hydrogen bond acceptor, molecular weight, lipophilicity, interacting residues, and distance, are tabulated. The amino acids that are involved in the interaction are also tabulated (Table 1).

Molecular dynamics simulation

Biochemical macromolecules are highly flexible, particularly in interactions with proteins and ligands. The online tool iMODs analyses this flexibility using the elastic network model (ENM) and normal-mode analysis (NMA), a method that studies molecules' actual movements. It calculates a wide range of values, including the Eigen values and graphed data, B-factor graphs, and RMS values that indicate distances between atoms and structural changes. The covariance matrix indicated relative displacements of either part of the protein-ligand complex concerning each other in its motion[34-35].

Results and Discussion

Molecular interaction of receptor-ligand

All the bioactive components present in the leaf of the *Mentha X piperita* are selected, and their drug - likeliness properties are checked first. There were about 67 bioactive components present in the leaf of the *Mentha X piperita* plant, and of that, 59 molecules passed Lipinski's rule and were selected for molecular docking. Blind docking was performed for all 59 molecules, and the affinity score is noted and the results are shown in (Suppl. Tables S1-S3). The interaction of the protein-ligand complex is visualised using Biovia Discover Studios, and the 2D structure of the reaction is also observedfor the ligands that show high affinity to the selected receptor (Fig. 1). Luteolin and Eriodictyol are natural flavonoids available in several fruits, vegetables and herbal plants. Particularly, Luteolin can cross blood blood-brain barrier that making it a potential therapeutic candidate for central nervous system disorders[36]. Eriodictyol plays an important therapeutic role in neuroprotection as well as exhibiting cardioprotective, hepatoprotective and antidiabetic activity[37]. Molecular docking results showed that these two compounds

Table 1 — Molecular docking score of the Receptor-ligand complex

Receptor	Ligand	Lipinski's rule	Docking score (Kcal/mol)	Number of hydrogen bond donors	Number of hydrogen bond acceptors	No. of Hydrogen bonds	Molecular weight	LogP-Lipophilicity	Interacting residues
$5HT_{1A}$	Luteolin	Passed	-8.6	4	6	2	286.24	2.28	CYS 148 LEU190, ARG150
	Eriodictyol	Passed	-8.4	4	6	2	288.26	2.22	CYS 148, ARG150LE U 190
$5HT_{1F}$	Eriodictyol	Passed	-8.4	4	6	1	288.26	2.22	LYS 35 ALA 30
	Luteolin	Passed	-8.9	4	6	2	286.24	2.28	SER 189 ARG 150, ALA 231 ILE 232
RAMP	Eriodictyol	Passed	-7	4	6	1	288.26	2.22	TYR 66 VAL99 PHE 93

showed the highest affinity to the selected receptors. Considering their pharmacological activity and molecular interactions, these two are selected for further study. However, Eriodictyol did not show interaction with RAMP. The amino acid residues involved in the interactions, hydrogen bonds and other bonds involved in the interactions are summarised in (Table 1). Interacting amino acids indicate that the active binding site of $5HT_{1A}$ is composed of the same set of amino acid residues. The 2-dimensional structures of ligand-target interactions are shown in (Fig. 1).

Normal mode analysis (NMA)

For a biological molecule to be flexible is a crucial factor. Flexibility of a biological molecule is important for interacting with protein-ligand interactions. Therefore, this online tool, iMODs, calculates the molecular motion and the structural flexibility through NMA study. The results are shown in (Figs. 2-6). NMA is a computational method used to study the dynamics and the flexibility of biological molecules. The server calculated the eigen values for each receptor-ligand complex, and they are represented in their respective table and pictures. The B-factor graph shows the average RMS value. Here, the RMS (Root mean square value) is used to measure the average distance between the atoms in the molecule, and they are also used for measuring any structural and conformational deviations. B-factor shows the stable structure of each docked molecule. The covariance matrix (blue and red colour plot) represents the correlated, uncorrelated motions of the protein-ligand complex. An elastic network model (grey colour plot) shows docked protein molecule (Cα) atoms are interconnected with "springs" of certain strengths (the darker grey representation of the stiffer springs). This ENM is used to study the protein-ligand complex's flexibility, stability and dynamics. And the springs in ENM represent the interaction between the atoms.

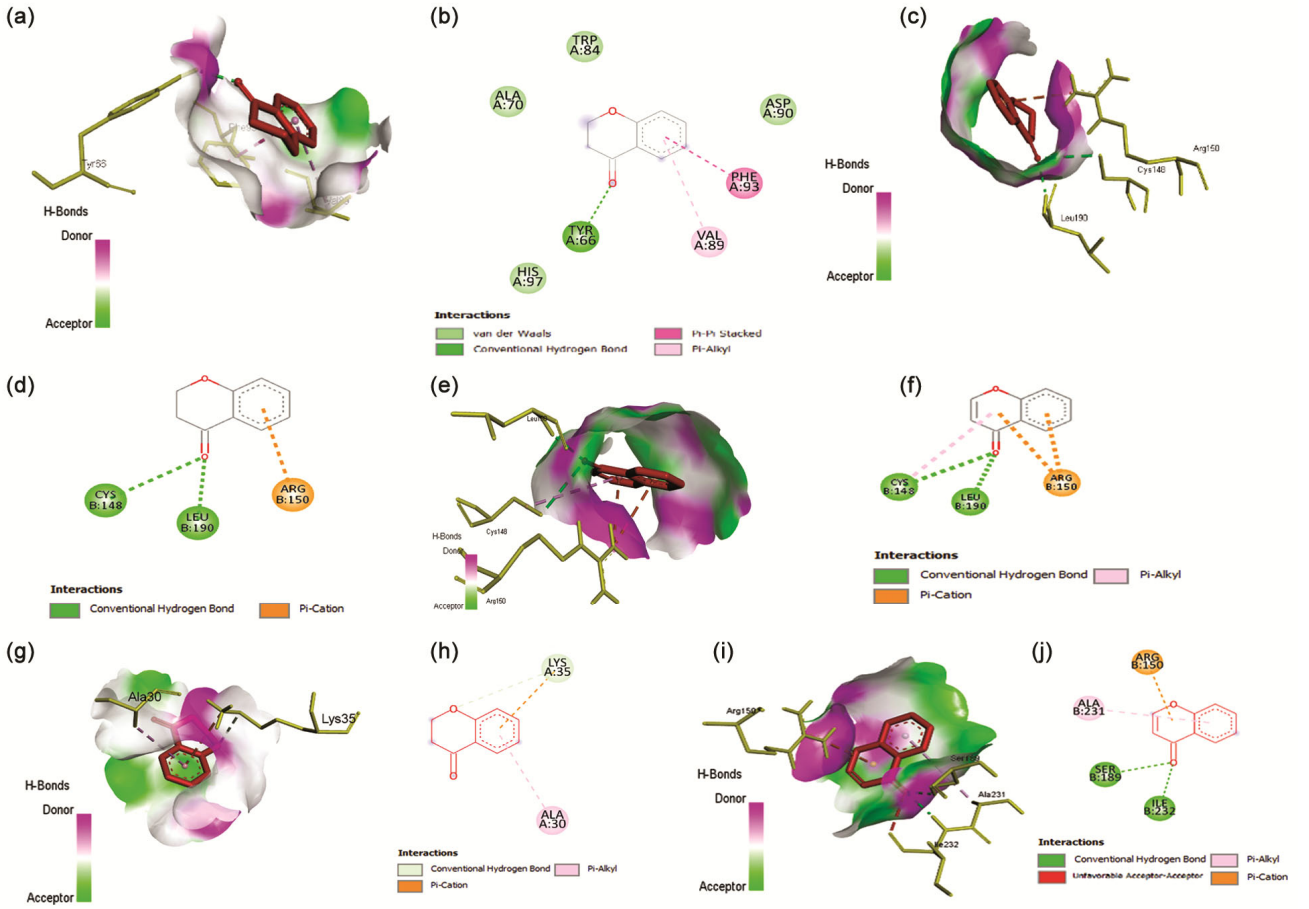

Fig. 1 — Molecular interaction of Ligand-Receptor complex: RAMP-Eriodictyol complex and interacting residues in (a & b); $5HT_{1A}$–Eriodictyol complex and interacting residues in (c & d); $5HT_{1A}$- Luteolin complex and interacting residues (e & f); $5HT_{1F}$-Eriodictyol complex and interacting residues in (g & i); and $5HT_{1F}$ – Luteolin complex and interacting residues in (i & j)

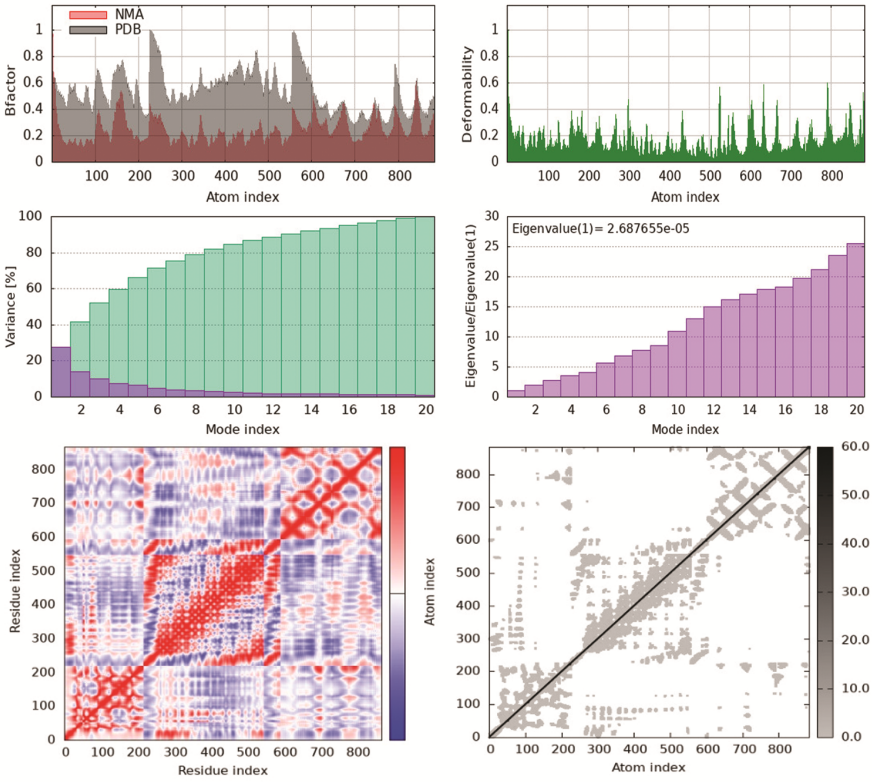

Fig. 2 — Normal mode analysis of molecular structure using iMOD: $5HT_{1A}$ and Luteolin

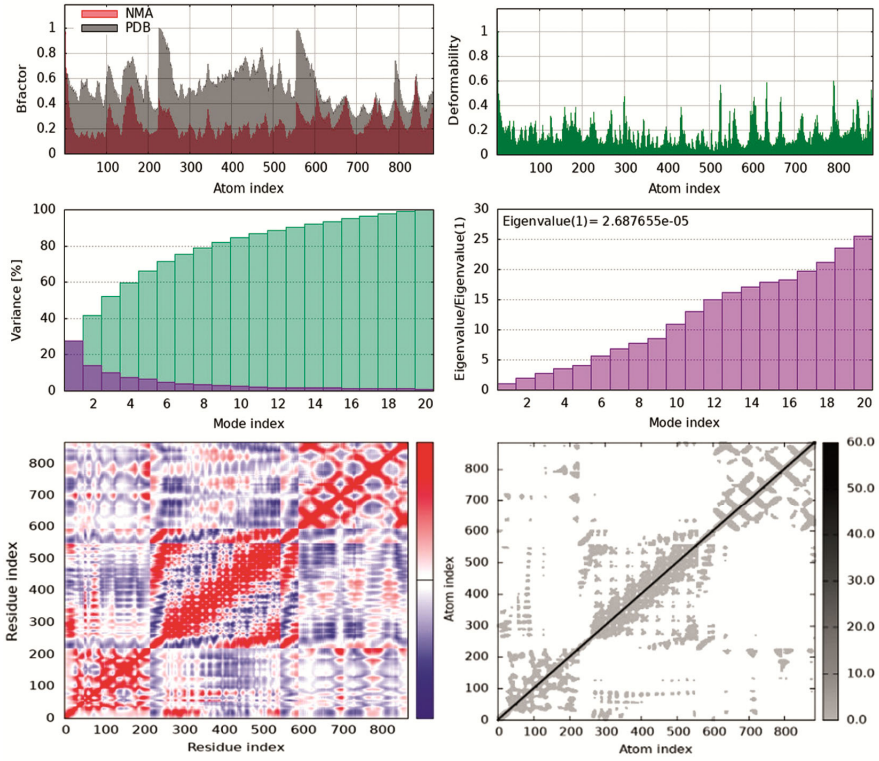

Fig. 3 — Normal mode analysis of molecular structure using iMOD: $5HT_{1A}$ and Eridocytol

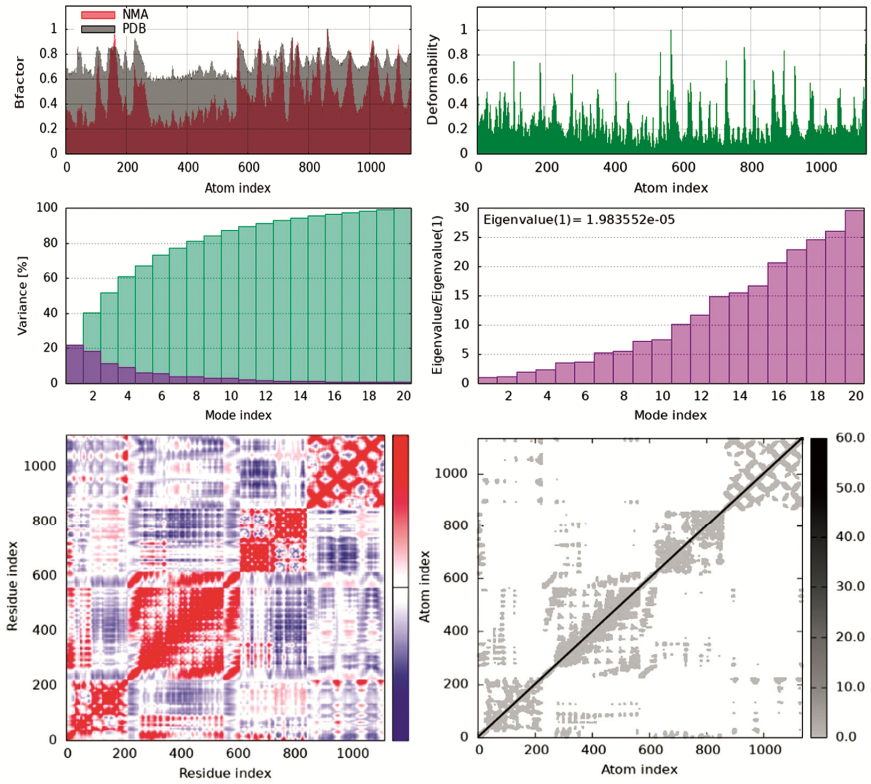

Fig. 4 — Normal mode analysis of molecular structure using iMOD: $5HT_{1F}$ and Eridocytol

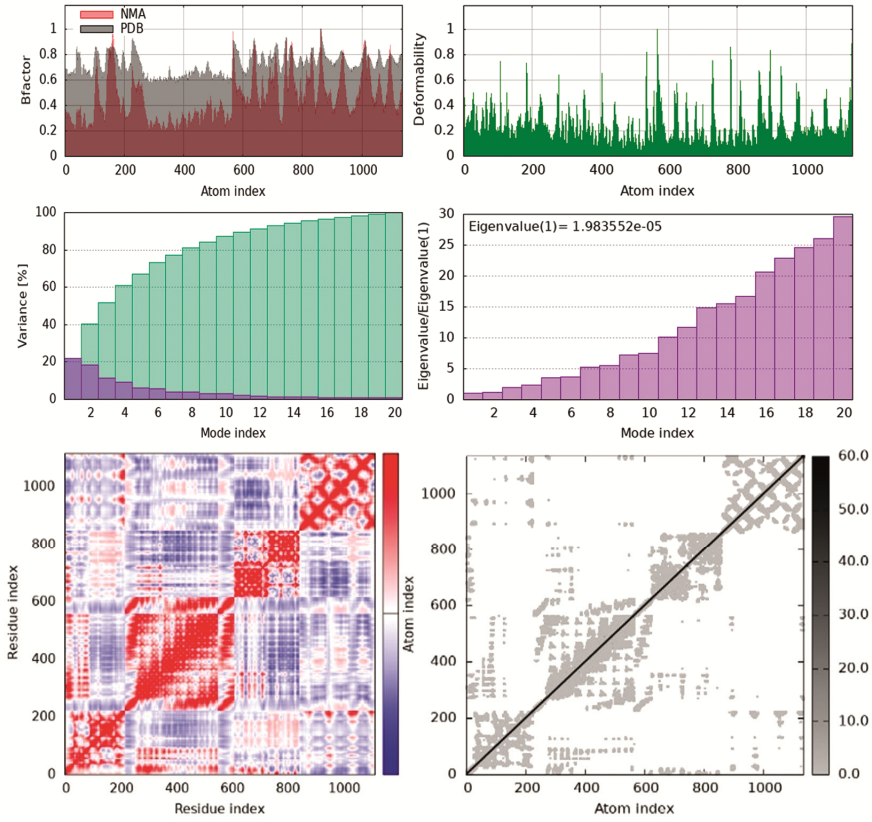

Fig. 5 — Normal mode analysis of molecular structure using iMOD: $5HT_{1F}$ and Luteolin

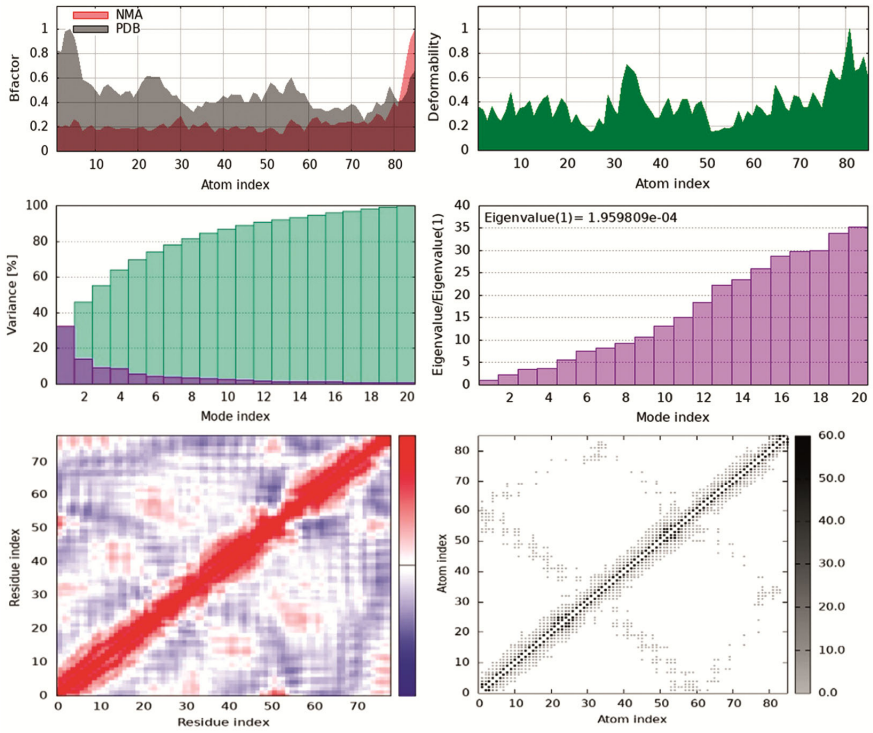

Fig. 6 — Normal mode analysis of molecular structure using iMOD: RAMP and Eriodicytol

Conclusion

Molecular docking was performed to explore the binding mechanism of ligands of *Mentha x pipertia* with the receptors $5HT_{1A}$, $5HT_{1F}$, and RAMP and correlate their docking score to decide good binding affinity ligands. The ligands are assessed with drug likeliness properties such as molecular weight, hydrogen bond acceptors, hydrogen bond donors, and logP (lipophilicity). The ligands Eridocytol and luteolin show drug-likeliness properties and good binding affinity. These ligands are further evaluated by their interaction with receptors $5HT_{1A}$, $5HT_{1F}$, RAMP, and the interacting amino acid residues, no of hydrogen bonds, and distance of hydrogen bonds are concluded. The stability of the interaction of ligand and protein is also visualised using an IModS online tool. We have evaluated these 2 ligands as the best druggable molecules and can be pointed out as the potential druggable molecules that can be used for the treatment of migraine.

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Conflict of interest

All authors declare no conflict of interest.

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