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In Silico Evaluation of Bioactive Compounds from *Monodora myristica (Gaertn.)* Dunal Essential Oil as MT_1 Melatonin Receptor Agonists for The Management of Insomnia

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ABSTRACT

Background: Sleep disorders remain a significant health challenge, with melatonin receptor 1 (MT_1) serving as a key target for pharmacological intervention. Previous *in vivo* study revealed that *Monodora myristica (Gaertn.)* Dunal essential oil prolonged total sleep time and reduced sleep latency in mice. This study investigated the potential of bioactive compounds from *Monodora myristica* essential oil as MT_1 agonists for sleep management, using *in silico* approaches.

Method: Dried seeds were extracted to yield 19.4% essential oil (110.24 g from 567 g powdered material). GC-MS was used to identify constituents. Molecular docking was done against human MT_1 crystal structure (PDB: 6ME5). Drug-likeness, pharmacokinetics, and toxicity of top compounds were predicted *in* silico.

Results: Twelve bioactive compounds were identified, with p-Cymene (31.16%), Tricyclene (17.35%), and alpha-Phellandrene (13.07%) as most abundant. Docking binding affinities ranged from -4.8 to -6.3 kcal/mol. Naphthalene had the strongest affinity (-6.3 kcal/mol), equal to melatonin (-6.3 kcal/mol), followed by p-Cymene (-5.9 kcal/mol). Caryophyllene and Alpha-Terpineol both scored -5.8 kcal/mol. Alpha-Terpineol had zero Lipinski violations, while Caryophyllene, p-Cymene, and Naphthalene had one each. All four had bioavailability score of 0.55 and good solubility. Alpha-Terpineol showed high GI absorption, BBB permeability, and minimal CYP450 inhibition; others had low GI absorption. Toxicity: p-Cymene was Class I, LD_{50} 3 mg/kg; Alpha-Terpineol was Class 5, LD_{50} 2830 mg/kg.

Conclusion: Alpha-Terpineol is the most promising candidate based on binding affinity, drug-likeness, pharmacokinetics, and low toxicity, and warrants further *in vitro* and *in vivo* validation for insomnia therapeutics.

Introduction

Sleep is a vital physiological process that plays an important role in maintaining overall health and cognitive performance [1]. With advancing research on the regulation of sleep, melatonin and its receptors have attracted considerable scientific interest for their involvement in sleep control. Melatonin, a synthetic analogue of the naturally occurring hormone, exerts its effects mainly through the MT_1 melatonin receptor [2]. The MT_1 melatonin receptor is a G protein-coupled receptor (GPCR) that regulates several intracellular signaling pathways upon activation by melatonin. When melatonin binds to MT_1, it triggers Gi/o proteins, which in turn suppress adenylate cyclase activity and reduce intracellular cAMP levels. The decline in cAMP subsequently lowers the activation of protein kinase A (PKA), affecting multiple downstream processes such as neuronal excitability and neurotransmitter release . MT_1 additionally engages other intracellular signaling pathways. For instance, it can stimulate phospholipase C (PLC), resulting in elevated intracellular calcium levels that further support its sedative actions. Activation of the MT_1 receptor has also been associated with increased release of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, thereby strengthening melatonin's sleep inducing effects[4]. Furthermore, MT_1 receptors are abundantly distributed throughout the brain, especially in areas that regulate sleep wake cycles, including the suprachiasmatic nucleus (SCN) and the thalamus. Their localization in these key regions highlights their critical role in circadian regulation and the maintenance of healthy sleep patterns [5].

In recent years, the exploration of bioactive compounds derived from natural sources has garnered attention for their potential therapeutic benefits without the side effects often associated with synthetic drugs[2]. Among these natural sources, *Monodora myristica* has shown promise due to its rich composition of essential oils and bioactive constituents. *Monodora myristica* is a tropical tree native to West Africa and is recognized for its aromatic seeds, which are used in culinary and traditional medicine. Ethnopharmacologically, the aromatic seed powder of *M. myristica* is traditionally employed as a flavor-enhancing agent in baked products, soups, and pastries. It is also incorporated into pepper soup as a stimulant and used in traditional medicine for the management of constipation and postpartum uterine hemorrhage in women[6]. According to Afolabi et al[7], *M. myristica* has been reported to possess therapeutic potential in the management of conditions including toothache, skin disorders, fever, and dysentery.

Despite the documented folkloric applications, only a limited number have been substantiated by scientific evidence [8]. Scientifically, *M. myristica* has been documented to exhibit a range of biological activities, notably antioxidant, antibacterial, and antidiabetic properties[9,10]. Okpoghono et al.[11] examined the potential use of bioactive constituents of *M. myristica* as dietary supplements, with results indicating that these compounds could be moderately incorporated into food formulations. Furthermore, the methanol seed extract of *M. myristica* was assessed for its anti-inflammatory activity and its effects on hematological parameters, demonstrating attenuation of hematological disturbances and suppression of lead acetate–induced leukocytosis. [12] In another study, Afolabi et al.[8] investigated the COX-2 inhibitory potential of bioactive compounds present in the essential oil of *M. myristica* using molecular docking and *in silico* toxicity analyses. Their findings revealed that the seed essential oil contained compounds such as naphthalene and 2,3,5,6-tetramethylphenol, which exhibited promising anti-inflammatory activity along with a favorable ADMET profile. Previous *in vivo* study by Afolabi et al., revealed that essential oil of showed significant ($p<0.05$) reduction in sleep latency and prolongation of total sleep time suggesting that it has hypnotic effect.[13]

Despite the extensive scientific evidence available on *M. myristica* seed extracts, the mechanistic action of bioactive constituents from the dried seed essential oil on the melatonin receptor 1 (MT_1), a key regulator of prolonged sleep, has not yet been validated. Accordingly, this study aims to evaluate the potential of bioactive compounds in the essential oil of *M. myristica* as MT_1 modulators using molecular docking approaches, with the objective of elucidating their role in prolonged sleep regulation and their underlying mechanisms of action. Additionally, the *in silico* toxicity profiles of the identified compounds will be assessed. The findings of this study are expected to provide a robust scientific basis for the isolation and future development of safe and effective bioactive compounds from the dried seed essential oil of *M. myristica* as promising MT_1 prolonged sleep regulators.

MATERIALS AND METHODS

Seed collection and identification

The dried seeds of *M. myristica* were collected and authenticated by Mr. I. I. Ogunlowo, Herbarium Officer, Department of Pharmacognosy, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria, where a voucher specimen was deposited. The Faculty of

Pharmacy Herbarium (FPI) is listed in the online edition of the Index Herbariorum under the accession number FPI 2111.

Extraction and distillation procedure

Hydro-distillation was carried out using a Clevenger type apparatus at the Postgraduate Toxicology Laboratory, Department of Biochemistry, Faculty of Science, Obafemi Awolowo University, Ile-Ife, Nigeria. A total of 567 g of dried *M. myristica* seeds was subjected to hydro-distillation for approximately 4 h. The essential oil obtained was collected, dried over anhydrous sodium sulfate, and stored in an amber-colored bottle at 4°C. The density of the oil was determined, and the percentage yield (Table 1) was subsequently calculated as follows:

$$\text{Percentage yield of the oil} = \frac{\text{Volume of oil obtained}}{\text{Weight of dried seed}} \times 100\%$$

Gas chromatography-mass spectrophotometric analysis.

The constituents of the crude oil extract done at the Central Research Laboratory, Ilorin were characterized using GC-MS (QP2010) MS-5973-634071 series under the following analytical conditions: the column oven temperature was initially set at 70.0 °C and increased to 280 °C within 5 minutes at a flow rate of 10 ml/min. The injection was performed at 250.0 °C using split flow injection with linear velocity flow control. The column pressure was maintained at 116.9 kPa, with a total flow rate of 40.8 ml/min, a column flow of 1.80 ml/min, and a linear velocity of 49.2 cm/s. A purge flow of 3.0 ml/min and a split ratio of 20.0 were employed. The ion source temperature was set at 200.0 °C, while the interface temperature was maintained at 250.0 °C, with a solvent cut time of 2.5 minutes. Mass spectrometric analysis commenced at 3.0 minutes and ended at 24.0 minutes, with a scan event time of 0.5 seconds and a scan speed of 666. The scan range was set between m/z 30.00 and 350.00. The compounds were identified and characterized using their gas chromatography retention times, while mass spectra were matched through computer-assisted comparison with reference standards from the NIST14 compound library.

***In silico* evaluation**

Ligand and target protein selection

The twelve ligands identified through GC–MS analysis of the essential oil from dried seeds of *M. myristica*, along with the standard drug melatonin, were retrieved from the PubChem database (http://pubchem.ncbi.nlm.nih.gov) and converted from Structured Data File (SDF) to Protein Data Bank (PDB) format. The crystal structure of the human target protein, melatonin receptor (MT_1) (PDB ID: 6ME5), was obtained from the Protein Data Bank (https://www.rcsb.org) and stored in PDB format.

Molecular docking

The molecular docking analysis was carried out as previously described [14] using AutoDock (v4.2) integrated within the PyRx platform (v0.8, Windows). Docking was performed with an exhaustiveness parameter of 8, generating nine binding conformations for each protein. The conformation with the lowest binding energy (most negative value) was selected to represent the ligand–receptor interactions. Visualization of the docking results was performed with Biovia Discovery Studio (v21.1.0.20289). The four ligands with the most favorable binding energies, along with the reference drug melatonin, were further analyzed and illustrated in both 2D and 3D formats.

ADMET evaluation

The four compounds exhibiting the highest binding free energies, together with melatonin, were further evaluated for their pharmacokinetic and safety profiles using ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis. ADEMT predictions were conducted employing the Protox-3.0 web server.
(https://tox.charite.de/protox3/index.php?site=compound_input).

Results

Gas chromatography-mass spectrometric analysis (GCMS)

Table 2 summarizes the retention times, peak areas, and systematic names of the compounds identified from the dried seed extract of *M. myristica* by GC–MS analysis. A total of twelve phytoconstituents were detected, with *p*-cymene (31.16%), tricyclene (17.35%), α-phellandrene (13.07%), and linalool (11.45%) as the predominant components. Minor constituents, occurring at less than 6%, included α-thujene, (±)-β-pinene, α-terpineol, caryophyllene, naphthalene, 4-carene, and tetramethylphenol. Furthermore, the total ion chromatogram (TIC) displayed several distinct peaks, each corresponding to volatile constituents eluting at specific retention times (Fig.1). Also, prominent peaks were observed at retention times 6.363, 9.328, 10.404, 13.751, 17.047, 24.147, 26.787, 27.174, 27.487, 38.226, and 39.469 minutes, indicating the presence of multiple abundant

compounds. The most dominant peak occurred at 10.404 minutes, suggesting that this compound constitutes the major component of the essential oil. Additional prominent peaks at 9.328 and 13.751 Minutes point to other compounds present in appreciable amounts, whereas smaller peaks distributed throughout the chromatogram represent minor phytochemical constituents (Fig. 1).

Table 1: Percentage yield of dried seed of *M. myristica*

	Powder plant material	Yield obtained
Mass (g)	567	110.24
Percentage yield (%)		19.4

Table 2: Compounds identified by GC-MS analysis of dried seed extract of *M. myristica*

S/No	Retention Time	% Peak area	Systematic name	Compo und name
1	6.069	5.88	Bicyclo[3.1.0] hex -2-ene, 4-methyl-(1-methylethyl) -	alpha-thujene
2	6.363	17.35	Tricyclo[2.2.1.0(2,6)] heptane, 1,7,7 -trimethyl-	Tricyclene
3	7.939	1.38	Bicyclo [3.1.1] heptane, 6,6 -dimethy 15908 018172 -67-3 97 l-2-methylene-, (1S)-	(±)-β-Pinene
4	9.328	13.07	alpha-Phellandrene	alpha-Phellandrene
5	10.404	31.16	p-Cymene	p-Cymene
6	13.751	11.45	1,6-Octadien-3-ol, 3,7-dimethyl -	Linalool
7	14.282	1.65	(1R,4R) -1-methyl -4-propan -2-ylcyclohex -2-en-1-ol	2-Cyclohexen-1-ol
8	17.047	2.58	Alpha-Terpineol	*α-Terpineol*
9	24.141	1.28	Caryophyllene	Caryophyllene
10	26.787	1.03	Naphthalene	Naphthalene
11	38.228	1.40	4-Carene, (1S,3R,6R) -(-)-	4-Carene
12	38.490	2.15	Phenol,2,3,5,6 -tetramethyl-	Phenol

Molecular docking analysis

The molecular docking study of bioactive compounds identified in the essential oil of *Monodora myristica* seeds revealed notable binding interactions with the target protein, with docking scores ranging between –4.8 and –6.3 kcal/mol (Table 3). Among the tested bioactive compounds, Caryophyllene (–5.8 kcal/mol), Alpha-Terpineol (–5.8 kcal/mol), p-Cymene (–5.9 kcal/mol), and Naphthalene (–6.3 kcal/mol) exhibited the strongest binding affinities, which were comparable to melatonin (–6.3 kcal/mol) (Table 4).

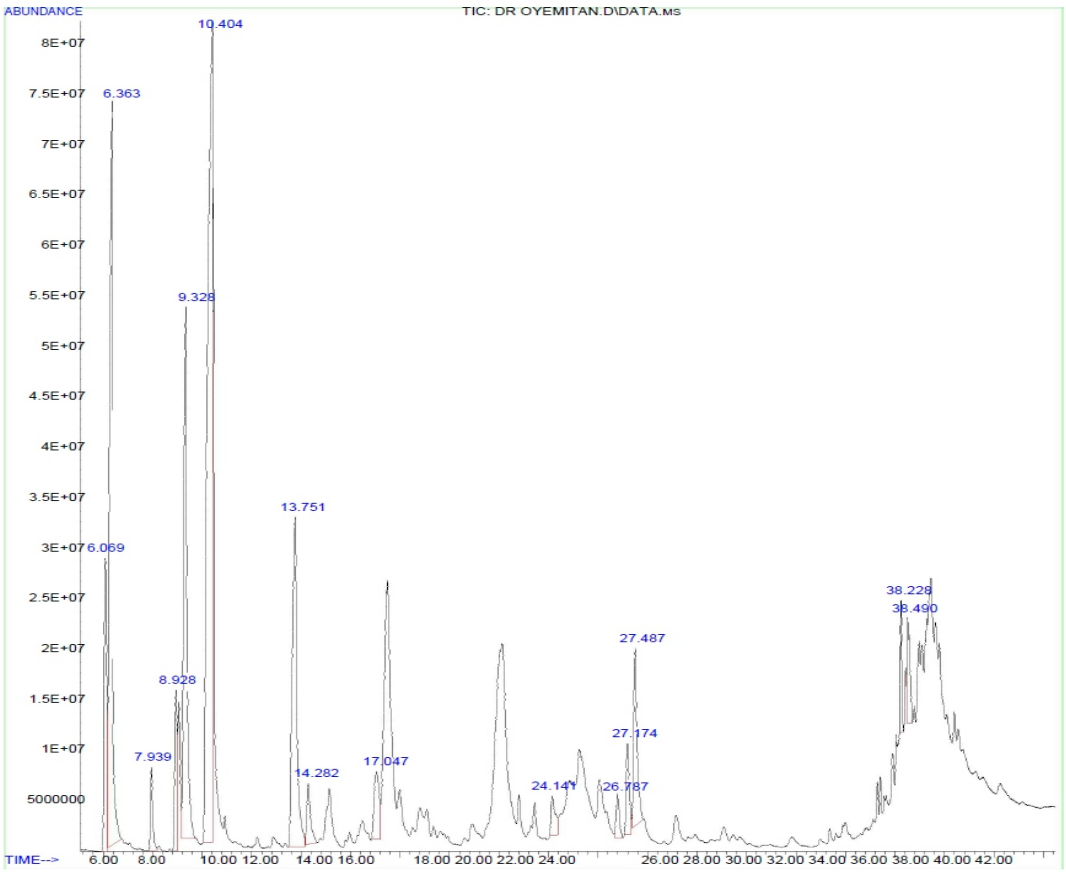

Fig. 1: GC-MS chromatogram of bioactive compounds identified from the dried seed of *M. myristica*

Post-docking analysis

The post-docking analysis illustrated the binding interactions between naphthalene and the active site residues of the target protein (6ME5) (Fig. 2). Molecular docking analysis revealed that naphthalene (CID: 931) occupies a well-defined hydrophobic cavity within the orthosteric binding site of the human melatonin receptor MT1 (PDB ID: 6ME5). The ligand was predominantly stabilized through aromatic and hydrophobic interactions**,** with π–π stacking contacts observed with TYR147 and ILE123**,** exhibiting interaction distances of 4.54–4.85 Å**,** consistent with favorable aromatic stacking. In addition, van der Waals interactions involving PHE65, GLY120, LEU127, TYR139, and ILE151 further contributed to the stabilization of the ligand within the binding pocket. The absence of hydrogen bonding interactions suggests that ligand recognition is largely driven by hydrophobic packing and π–π interactions**,** which are characteristic features of MT_1 receptor–ligand binding. Collectively, these interaction profiles indicate a stable accommodation of naphthalene within the MT_1 receptor and support its potential relevance in modulating receptor activity.

Figure 3 illustrates the binding mode and key intermolecular interactions of *p*-cymene (CID: 7463) within the orthosteric binding pocket of the human melatonin receptor MT_1 (PDB ID: 6ME5). Molecular docking analysis revealed that *p*-cymene is stably accommodated in a predominantly hydrophobic cavity formed by residues ILE123, ILE 151, PHE 65, TYR 147, GLY120, LEU 127, and TYR 139. The ligand establishes multiple alkyl and π–alkyl interactions with ILE 123 and ILE 151, contributing to hydrophobic stabilization of the complex. Notably, π–σ and π–π stacking interactions were observed between the aromatic ring of *p*-cymene and the aromatic side chains of PHE 65 and TYR 147, respectively, indicating favorable aromatic complementarity within the binding site. Additional van der Waals contacts with surrounding residues further reinforced ligand–receptor affinity. Collectively, these interactions suggest that *p*-cymene exhibits a favorable binding orientation and interaction profile within the MT_1 receptor, supporting its potential modulatory role on melatonin receptor activity.

Table 3. The Docking Score (kcal/mol) of the Bioactive Compounds Identified in Essential Oil of Dried Seed of *Monodora Myristica* Against Human Melatonin Receptor 1 (MT_1)

S/N	Systemic Name	Compound Name	PubChem CID	Docking Score (kCal/mol) PDB ID: ID:6MES
1	Bicyclo[3.1.0]hex -2-ene, 4-methyl-(1-methylethyl) -	alpha-thujene	17868	-5.4
2	Tricyclo[2.2.1.0(2,6)]heptane, 1,7,7 -trimethyl-	Tricyclene	79035	-5.2
3	Bicyclo[3.1.1]heptane, 6,6 -dimethy 15908 018172 -67-3 97 l-2-methylene-, (1S)-	(±)-β-Pinene	14896	-5.0
4	alpha-Phellandrene	alpha.-Phellandrene	7460	-4.8
5	**p-Cymene**	**p-Cymene**	**7463**	**-5.9**
6	1,6-Octadien-3-ol, 3,7-dimethyl-	Linalool	6549	-5.4
7	(1R,4R)-1-methyl-4-propan-2-ylcyclohex-2-en-1-ol	2-Cyclohexen-1-ol	122485	-5.6
8	**Alpha-Ter pineol**	***α-Terpineol***	**17100**	**-5.8**
9	**Caryophyllene**	**Caryophyllene**	**5281515**	**-5.8**
10	**Naphthalene**	**Naphthalene**	**931**	**-6.3**
11	4-Carene, (1S,3R,6R) -(-)-	4-Carene	530422	-5.6
12	Phenol,2,3,5,6 -tetramethyl-	Phenol	10694	-5.5
		Standard Drug		
*	***N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]acetamide**	**Melatonin**	**896**	**-6.3**

Key: * represents the standard drug

Table 4: The binding energy of the top four compounds identified in essential oil of dried seed of *Monodora Myristica*

S/N	Systemic Name	Compound Name	PubChem CID	Docking S core (kCal/mol)
1	Alpha -Terpineol	*α-Terpineol*	17100	-5.8
2	Caryophyllene	Caryophyllene	5281515	-5.8
3	p-Cymene	p-Cymene	7463	-5.9
4	Naphthalene	Naphthalene	931	-6.3
		Standard Drug		
	N-[2-(5-methoxy -1*H*-indol-3-yl)ethyl]acetamide	Melatonin	896	-6.3

Figure 4 depicts the binding conformation and intermolecular interactions of Caryophyllene, within the active site of the human melatonin receptor MT_1. Docking analysis showed that Caryophyllene occupies a hydrophobic region of the receptor cavity, engaging predominantly in non-polar interactions with surrounding residues. A key alkyl interaction was observed between Caryophyllene and ALA 190, suggesting a stabilizing hydrophobic contact that anchors the ligand within the binding pocket. Additional van der Waals interactions were formed with PRO 161, TYR 187, VAL 191, ALA 158, PHE 194, and HIS 195, collectively contributing to ligand accommodation and binding stability. The absence of polar or hydrogen-bond interactions indicates that hydrophobic forces primarily govern the Caryophyllene MT_1 receptor association. Above all, the interaction profile supports a favorable binding orientation of Caryophyllene within the MT1 receptor, highlighting its potential relevance in melatonin receptor modulation.

Figure 5 illustrates the molecular interaction of caryophyllene with the human melatonin receptor (MT_1; PDB: 6ME5). Caryophyllene was favorably accommodated within the receptor binding pocket, forming a single alkyl interaction with ALA190 at an interaction distance of 5.03 Å. Additional van der Waals interactions were observed with ALA158, PRO161, TYR187, VAL191, PHE194, and HIS195, which collectively stabilized the ligand within the binding cavity. No conventional hydrogen bonds were detected, indicating that the ligand receptor complex was predominantly maintained through hydrophobic interactions. The 3D and 2D interaction profiles demonstrate that caryophyllene exhibits a stable binding orientation within the MT_1 receptor, supported primarily by alkyl and van der Waals contacts.

Figure 6 illustrates the binding conformation and key molecular interactions of melatonin within the active site of the human melatonin receptor MT_1, presented in both 3D and 2D representations. Melatonin was well accommodated in the receptor binding pocket, forming a stable interaction network involving hydrogen bonding, π-interactions, and hydrophobic contacts. Notably, melatonin established conventional hydrogen bonds with ASN 60 (3.74 Å) and ASN 63 (4.43 Å), which are critical residues implicated in ligand recognition and receptor activation. Additional stabilizing hydrogen bond interactions were observed with ASN 301 (3.91 Å) and ASP 299, further anchoring the ligand within the binding cavity. The indole aromatic ring of melatonin participated in π–π T-shaped interactions with TRY128 (7.69 Å) and PHE 237 (5.83–6.25 Å), contributing significantly to binding stabilization through aromatic stacking. Furthermore, π-alkyl interactions with TYR128 and PHE 237, alongside van der Waals contacts involving ARG125, LEU 58, GLN 300, Asp233, and ARG 235, collectively enhanced the hydrophobic complementarity of the ligand receptor complex. These interactions underscore the favorable orientation of melatonin within the MT_1 receptor and highlight residues essential for high affinity binding. Overall, the observed interaction profile corroborates the known pharmacological relevance of melatonin toward MT_1, validating the docking protocol and providing a structural basis for comparing the binding behavior of other test compounds investigated in this study.

ADMET analysis of the identified compounds

Drug-likeness prediction output and physiochemical properties of the top four bioactive compounds identified from essential oil of *Monodora myristica* dried seed

Table 5 summarizes the drug-likeness and physicochemical properties of the top bioactive constituents identified from the essential oil of *Monodora myristica* dried seed, with melatonin included as the reference compound. Molecular docking revealed binding energies ranging from −5.8 to −6.3 kcal/mol. Naphthalene and melatonin exhibited the strongest binding affinity (−6.3 kcal/mol), followed by *p*-cymene (−5.9 kcal/mol), while α-terpineol and caryophyllene showed comparable affinities (−5.8 kcal/mol). All four top essential oil constituents possessed low molecular weights (128.17–204.35 g/mol), consistent with favorable permeability profiles, whereas melatonin recorded a molecular weight of 232.28 g/mol. Hydrogen bond analysis showed that α-terpineol was the only essential oil constituent with hydrogen-bonding capability (one donor and one acceptor), in contrast to melatonin, which exhibited two donors and two acceptors; no hydrogen bond interactions were observed for caryophyllene, *p*-cymene, or naphthalene. The number of rotatable bonds was minimal among the essential oil constituents (0–1), whereas melatonin contained five rotatable bonds. Lipophilicity values (iLogP o/w) ranged from 1.99 to 3.25, remaining within acceptable limits (< 5) for oral drug candidates. Polar surface area analysis revealed moderate polarity for α-terpineol (TPSA = 20.23 $Å^2$) and higher polarity for melatonin (54.12 $Å^2$), while caryophyllene, *p*-cymene, and naphthalene exhibited zero TPSA. According to Lipinski's Rule of Five, α-terpineol and melatonin showed no violations, whereas caryophyllene, *p*-cymene, and naphthalene each presented a single violation.

Predicted lipophilicity (log p), water solubility (log S (Slicos-IT)), and bioavailability scores of essential oils of *Monodora Myristica* dried seed

Table 6 presents the predicted lipophilicity, water solubility, and oral bioavailability scores of the top four bioactive essential oil constituents of *Monodora myristica* dried seed, with melatonin included as the reference compound. The consensus log P o/w values of the essential oil constituents ranged from 2.58 to 4.24, with α-terpineol exhibiting the lowest lipophilicity and caryophyllene the highest, while melatonin (standard drug) recorded a lower log P o/w value of 1.83. Water solubility predictions (log S, Silicos-IT) varied from −1.69 to −4.03 among the top four essential oil constituents, classifying α-terpineol, caryophyllene, and *p*-cymene as soluble, whereas naphthalene was predicted to be moderately soluble. In contrast, melatonin showed lower aqueous solubility (log S = −4.62) and was classified as moderately soluble. Despite differences in lipophilicity and solubility profiles, all evaluated compounds demonstrated identical bioavailability scores (0.55), indicating comparable predicted oral bioavailability. Notably, α-terpineol displayed a favorable balance between moderate lipophilicity and higher predicted solubility relative to the other essential oil constituents.

Pharmacokinetics prediction output of the top four bioactive essential oils of *Monodora Myristica* dried seed

Table 7 summarizes the predicted pharmacokinetic properties of the top four bioactive essential oil constituents of *Monodora myristica* dried seed, with melatonin included as the reference compound. Gastrointestinal (GI) absorption was predicted to be high for α-terpineol and melatonin, whereas caryophyllene, *p*-cymene, and naphthalene exhibited low GI absorption. Blood–brain barrier permeability was predicted for α-terpineol, *p*-cymene, naphthalene, and melatonin, while caryophyllene was not brain-penetrant. None of the evaluated compounds were predicted to be substrates of P-glycoprotein. Cytochrome P450 inhibition profiling revealed that α-terpineol showed no inhibitory activity against the assessed CYP isoforms. In contrast, caryophyllene was predicted to inhibit CYP2C19 and CYP2C9, *p*-cymene inhibited CYP2D6, and naphthalene inhibited CYP1A2. Melatonin was predicted to inhibit CYP1A2 only. Skin permeation values [log Kp (cm/s)] ranged from −4.21 to −4.83 for the essential oil constituents, with *p*-cymene showing the highest skin permeability, while melatonin exhibited the lowest skin permeation (−6.59).

Toxicity profile of the top four essential oils of *Monodora Myristica* dried seed

Table 8 presents the predicted toxicity profiles of the top four essential oil constituents of *Monodora myristica* dried seed, with melatonin included as the reference compound. All top four evaluated compounds were predicted to be blood–brain barrier permeant and non-cytotoxic. α-Terpineol and melatonin were classified as non-carcinogenic and non-immunotoxic, whereas caryophyllene showed predicted immunotoxicity without carcinogenic potential. In contrast, *p*-cymene and naphthalene were predicted to be carcinogenic but non-immunotoxic. Acute toxicity classification revealed that α-terpineol exhibited an LD_{50} of 2830 mg/kg and was assigned to toxicity class 5, indicating low acute oral toxicity. Caryophyllene showed an LD_{50} of 5300 mg/kg and was also classified as class 5. Naphthalene demonstrated moderate acute toxicity with an LD_{50} of 316 mg/kg (class 4), comparable to melatonin, which showed an LD_{50} of 963 mg/kg (class 4). In contrast, *p*-cymene exhibited high acute toxicity with an LD_{50} of 3 mg/kg and was classified as class I, indicating severe toxicity upon oral exposure.

Discussion

The extraction process constitutes a fundamental and highly effective strategy for releasing phytocompounds embedded within plant matrices. These compounds, extensively documented across diverse scientific disciplines for their broad spectrum of biological and pharmacological activities[18], are collectively classified as phytochemicals or plant-derived organic constituents. In our previous investigation, extraction of *Monodora myristica* dried seeds yielded 19.4% from an initial 567 g of starting material.[15] The extracted constituents were subsequently characterized using advanced spectroscopic techniques, specifically gas chromatography–mass spectrometry (GC–MS).

Comprehensive GC–MS profiling of *M. myristica* dried seeds previously identified twelve bioactive constituents, with *p*-cymene, tricyclene, α-phellandrene, and linalool emerging as the predominant compounds, collectively accounting for approximately 70% of the total composition. [15]These bioactive molecules were further evaluated using computer-aided drug discovery (CADD) approaches, including molecular docking, to assess their interactions with inflammatory molecular targets. [18] Building on these findings, the present study investigates the therapeutic potential of bioactive constituents from *M. myristica* essential oil against the melatonin receptor (MT_1), with the objective of elucidating their relevance for prolonged sleep

management through *in silico* evaluation.

The docking analysis of bioactive constituents from the essential oil of *Monodora myristica* dried seeds against the human melatonin receptor 1 (MT_1, PDB ID: 6MES) revealed distinct variations in predicted binding affinities, as summarized in Table 3. Docking scores, expressed in kcal/mol, provide an *in silico* estimate of the thermodynamic favorability of ligand–receptor interactions, with more negative values indicative of stronger binding. Among the compounds tested, Naphthalene exhibited the most favorable docking score (−6.3 kcal/mol), equivalent to that of the standard ligand melatonin (−6.3 kcal/mol), suggesting a comparable potential for receptor engagement. A similar trend was observed among the four top-scoring compounds occupying the same binding pocket of the melatonin receptor 1, with Naphthalene being notably included (Table 4). This observation indicates that Naphthalene may occupy key hydrophobic pockets within the MT_1 binding site, potentially mimicking endogenous melatonin interactions. These findings were consistent with the previous study. [16] Other monoterpenes, including p-Cymene (−5.9 kcal/mol), α-Terpineol (−5.8 kcal/mol), and Caryophyllene (−5.8 kcal/mol), demonstrated moderate yet significant binding affinities. The structural characteristics of these compounds, particularly their cyclic hydrocarbon frameworks and hydrophobic moieties, likely facilitate van der Waals interactions and steric complementarity within the receptor's hydrophobic cavity. Conversely, compounds such as α-thujene (−5.4 kcal/mol), Tricyclene (−5.2 kcal/mol), and α-Phellandrene (−4.8 kcal/mol) exhibited relatively weaker interactions, which may reflect suboptimal orientation or lower complementarity with the receptor binding site.

Figure 2 depicts the molecular engagement between naphthalene (CID: 931) and the human melatonin receptor MT_1 (PDB ID: 6ME5), visualized through both three-dimensional (3D) and two-dimensional (2D) representations. The 3D model (left side) highlights the spatial accommodation of naphthalene within the receptor's transmembrane binding cavity, whereas the 2D schematic (right side) delineates the specific amino acid residues mediating ligand stabilization. The docking conformation demonstrates that naphthalene resides within a predominantly hydrophobic pocket formed by the α-helical transmembrane segments, in line with the canonical topology of G protein–coupled receptors (GPCRs). The planar aromatic framework of naphthalene facilitates its optimal insertion into the lipophilic core, supporting steric complementarity and stabilization via non-polar interactions. Key residues implicated in binding include Tyr-147, Ile-123, Ile-151, Phe-165, Gly-120, Leu-127, and Tyr-139. Notably, π–π stacking occurs with Tyr-147, while π–alkyl and π–sigma interactions engage hydrophobic residues such as Ile-123. Complementary van der Waals contacts with neighboring residues further reinforce ligand stability. The measured interaction distances (~4.54–4.85 Å) align with expectations for aromatic and hydrophobic contacts, consistent with the non-polar characteristics of naphthalene. This finding was consistent with a previous study. [15,16]

Figure 3 delineates the molecular interaction profile of p-cymene (CID: 7463) within the orthosteric binding cavity of the human melatonin receptor MT1 (PDB ID: 6ME5), presented in both three-dimensional (3D) and two-dimensional (2D) formats. The 3D structural representation demonstrates that p-cymene is favorably accommodated within the transmembrane domain of MT_1, exhibiting a conformational orientation consistent with steric complementarity and optimal cavity occupancy. This spatial integration suggests a stable ligand–receptor complex formation driven predominantly by hydrophobic forces. The 2D interaction model further elucidates the molecular determinants underlying ligand stabilization. p-Cymene engages primarily in van der Waals and π-alkyl interactions with key residues lining the hydrophobic pocket, including Ile151, Ile123, Gly120, Phe-65, Tyr-147, Leu-127, and Tyr-139. The involvement of aromatic residues such as phenylalanine and tyrosine underscores the contribution of π-mediated contacts in reinforcing ligand anchorage within the receptor core. Interaction distances ranging from approximately 3.9 to 5.1 Å fall within the accepted threshold for energetically favorable hydrophobic and π-interactions, thereby substantiating the structural stability of the complex. [17] Importantly, the absence of hydrogen bonding interactions is consistent with the non-polar chemical architecture of p-cymene, a monoterpenoid hydrocarbon lacking heteroatoms capable of forming classical electrostatic contacts. Consequently, ligand affinity appears to be governed predominantly by hydrophobic stabilization and shape complementarity rather than polar interaction networks. This observation aligns with the intrinsic physicochemical environment of G-protein-coupled receptor (GPCR) binding domains, which are typically enriched in lipophilic residues to facilitate interactions with hydrophobic ligands.[18]

The molecular docking analysis of α-Terpineol (CID: 17100) within the orthosteric binding pocket of the human melatonin receptor MT_1 (PDB: 6ME5) revealed a favorable binding conformation and key intermolecular interactions

that support potential receptor engagement. In the 3D complex (Fig. 4), α-Terpineol is situated in a predominantly hydrophobic transmembrane cavity, consistent with the lipophilic nature of melatonin receptor binding sites reported in prior structural studies of G-protein coupled receptors (GPCRs).[19] The orientation of α-Terpineol allows insertion of its aliphatic ring toward deep hydrophobic residues, suggesting efficient shape complementarity and structural accommodation.

Analysis of the 2D interaction structure (Fig. 4) highlights a conventional hydrogen bond between the hydroxyl group of α-Terpineol and the indole side chain of TRP-116 (distance ≈4.32 Å). This interaction aligns with the reported importance of conserved tryptophan residues in stabilizing GPCR ligands via polar contacts. [20] In addition to the hydrogen bond, multiple van der Waals interactions with Thr119, Gly120, Leu150, and Ile151 further reinforce the ligand's position within the pocket, consistent with hydrophobic anchoring mechanisms observed in class A GPCR activation. [21]

Hydrophobic π-interactions, including π-sigma and π-alkyl contacts with Tyr147 and Ile123 (distances 4.42–5.80 Å), dominate the nonpolar stabilization network. These interactions likely contribute significantly to binding affinity, in line with evidence that nonpolar contacts often drive the recognition of small lipophilic molecules in GPCR binding domains.[22] The cumulative interaction profile comprising both specific hydrogen bonding and extensive hydrophobic contacts suggests that α-Terpineol is capable of forming a stable complex with MT_1, potentially modulating receptor dynamics. Such binding characteristics support further investigation into α-Terpineol as a functional ligand or allosteric modulator of melatonin signaling pathways, with implications for chronobiological and neurophysiological regulation.[22]

MT_1 is a principal receptor involved in the regulation of circadian rhythm and sleep initiation. Activation of this receptor by endogenous melatonin promotes sleep onset by reducing neuronal excitability and synchronizing the sleep–wake cycle. [23] Therefore, the favourable accommodation of caryophyllene within the MT_1 binding pocket suggests that the compound may interact with melatonin signalling pathways associated with sleep regulation (Figure 5). This observation is consistent with previous reports describing caryophyllene as a bioactive sesquiterpene with anxiolytic and neuroprotective properties, both of which are closely linked to improved sleep quality. [24] Although molecular docking alone cannot confirm receptor activation, the stable interaction profile observed in Fig. 5 provides a plausible molecular basis for the potential sleep-promoting effects of caryophyllene. These findings suggest that caryophyllene may serve as a promising natural modulator of MT_1-mediated signalling and support its further investigation as a candidate for managing sleep disturbances and circadian rhythm disorders.

Table 5: Drug-likeness prediction output and physiochemical properties of the top bioactive compounds identified from essential oil of *Monodora myristica* dried seed

Compounds	Binding Energy (kcal/mol)	Molecular Weight (g/mol)	Hydrogen Bonds		Rotatable Bonds	iLog ($P_{o/w}$)	TPSA ($Å^2$)	Lipinski (RO5) Violation
			Donor	Acceptor				
Alpha -Terpineol	-5.8	154.25	1	1	1	2.51	20.23	0
Caryophyllene	-5.8	204.35	0	0	0	3.25	0.00	1
p-Cymene	-5.9	134.22	0	0	1	2.51	0.00	1
Naphthalene	-6.3	128.17	0	0	0	1.99	0.00	1
*Melatonin	-6.3	232.28	2	2	5	1.98	54.12	0

Key: * represents the standard drug

Table 6: Predicted lipophilicity (log p), water solubility (log S (Slicos-IT)), and bioavailability scores of the top four essential oils of *Monodora myristica* dried seed

Compounds	Binding Energy (kcal/mol)	Consensus Log P $_{o/w}$	Log S (Silicos - IT)	Solubility Class	Bioavailability Scores
Alpha -Terpineol	-5.8	2.58	-1.69	Soluble	0.55
Caryophyllene	-5.8	4.24	-3.77	Soluble	0.55
p-Cymene	-5.9	3.50	-3.57	Soluble	0.55
Naphthalene	-6.3	3.10	-4.03	Moderately soluble	0.55
*Melatonin	-6.3	1.83	-4.62	Moderately soluble	0.55

Key: * represents the standard drug

Table 7: Pharmacokinetics prediction output of the top four bioactive essential oils of *Monodora Myristica* dried seed

Compounds	Binding Energy (kcal/mol)	GI Absorption	Brain-Blood Permeant	Pgp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Skin Permeation [Log kp (cm/s)]
Alpha-Terpineol	-5.8	High	Yes	No	No	No	No	No	No	-4.83
Caryophyllene	-5.8	Low	No	No	No	Yes	Yes	No	No	-4.44
p-Cymene	-5.9	Low	Yes	No	No	No	No	Yes	No	-4.21
Naphthalene	-6.3	Low	Yes	No	Yes	No	No	No	No	-4.74
*Melatonin	-6.3	High	Yes	No	Yes	No	No	No	No	-6.59

Key: * represents the standard drug

Table 8: Toxicity profile of the top four essential oils of *Monodora Myristica* dried seed

Compounds	Binding Energy (kcal/mol)	BB-Barrier	Cytotoxicity	Carcinogenicity	Immunotoxicity	Toxicity Class
Alpha-Terpineol	-5.8	Active	Inactive	Inactive	Inactive	$LD_{50:}$ 2830 mg/kg, Class 5: may be harmful if swallowed (2000 < LD50 ≤ 5000)
Caryophyllene	-5.8	Active	Inactive	Inactive	Active	$LD_{50:}$ 5300 mg/kg, Class 5: may be harmful if swallowed (2000 < LD50 ≤ 5000)
p-Cymene	-5.9	Active	Inactive	Active	Inactive	LD_{50}:3 mg/kg, Class I: fatal if swallowed (LD50 ≤ 5)
Naphthalene	-6.3	Active	Inactive	Active	Inactive	LD_{50}: 316 mg/kg, Class 4: harmful if swallowed (300 < LD50 ≤ 2000)
* Melatonin	-6.3	Active	Inactive	Inactive	Inactive	LD_{50}: 963 mg/kg, Class 4: harmful if swallowed (300 < LD50 ≤ 2000)

Key: * represents the standard drug

Figure 6 shows that melatonin binds strongly within the active site of the human melatonin receptor (MT_1) through multiple hydrogen bonds, aromatic interactions, and van der Waals contacts. Conventional hydrogen bonds with ASN60, ASN63, and ASN301, together with π–π T-shaped and π–alkyl interactions involving TYR128 and PHE237, provide high binding affinity and stabilize the ligand within the receptor binding pocket. Additional van der Waals interactions further reinforce the ligand receptor complex. The extensive interaction network is consistent with melatonin's role as the endogenous MT_1 agonist and explains its high receptor affinity. [25] MT_1 activation is essential for regulating circadian rhythm and promoting sleep onset by synchronizing the sleep wake cycle. Thus, the stable binding of melatonin observed in Figure 6 provides a structural basis for its well-established sleep-promoting effects. This study was consistent with previous report.[25]

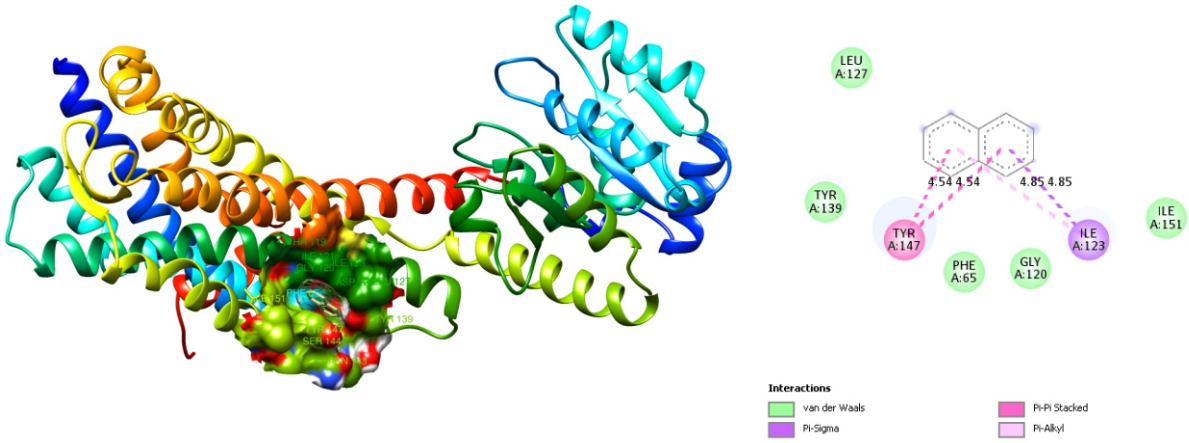

Fig. 2: The molecular interaction of amino acids residues of crystal structure of human melatonin receptor (MT_1) (PDB:6ME5) with Naphthalene (CID: 931), 3D left, 2D right

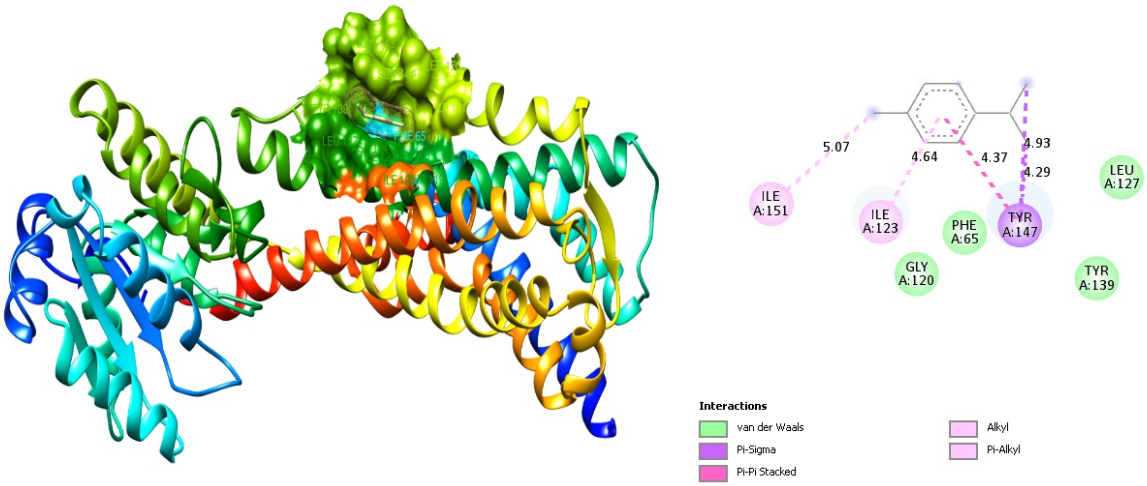

Fig. 3: The molecular interaction of amino acids residues of crystal structure of human melatonin receptor (MT_1) (PDB:6ME5) with p-Cymene (CID: 7463), 3D left, 2D right

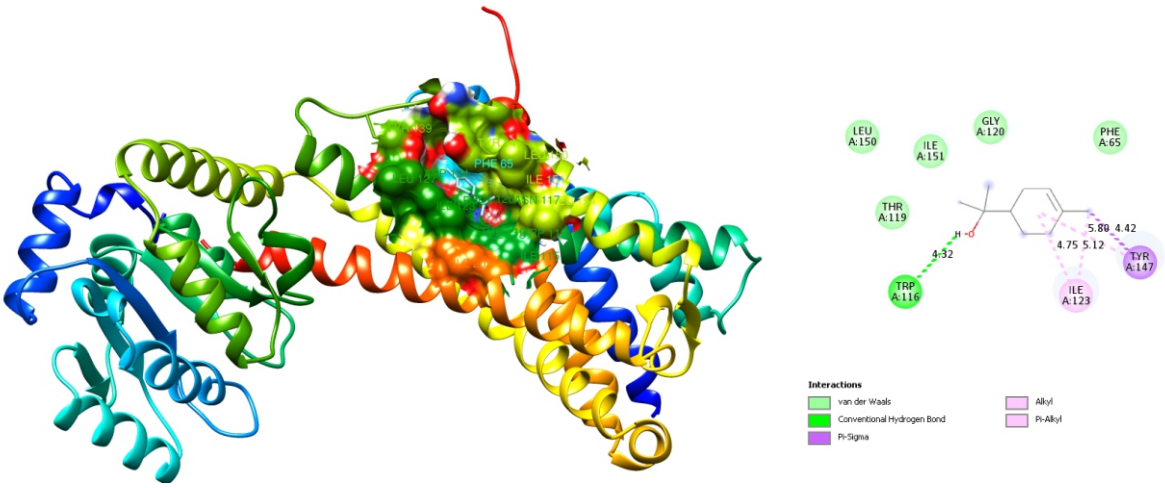

Fig. 4: The molecular interaction of amino acids residues of crystal structure of human melatonin receptor (MT_1) (PDB:6ME5) with Alpha-Terpineol (CID: 17100), 3D left, 2D right

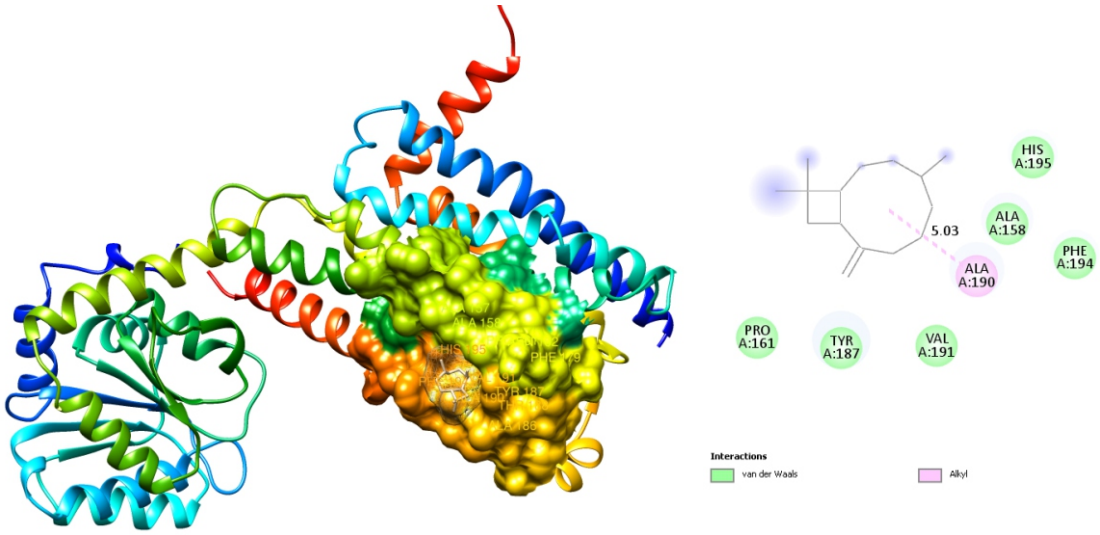

Fig. 5: The molecular interaction of amino acids residues of crystal structure of human melatonin receptor (MT_1) (PDB:6ME5) with Caryophyllene (CID: 5281515), 3D left, 2D right

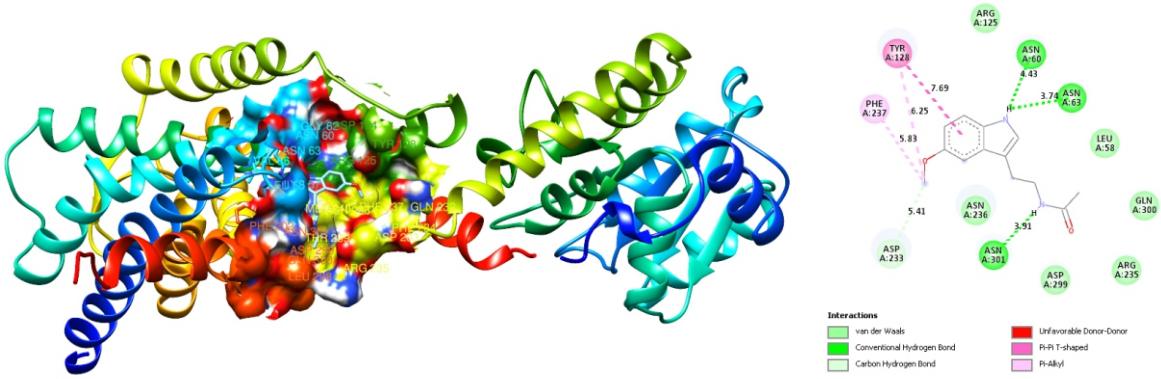

Fig. 6: The molecular interaction of amino acids residues of crystal structure of human melatonin receptor (MT_1) (PDB:6ME5) with Melatonin (CID: 896), 3D left, 2D right

The drug-likeness analysis indicated that the major phytochemicals from *Monodora myristica* essential oil possess favorable physicochemical properties for oral bioavailability. α-Terpineol showed the most balanced profile, satisfying Lipinski's rule of five with moderate lipophilicity, low molecular weight, and low TPSA, suggesting good membrane permeability.[15] Although caryophyllene, *p*-cymene, and naphthalene each exhibited one Lipinski violation, their low molecular weights and lipophilic nature may enhance passive diffusion across the blood–brain barrier, an important feature for MT_1-targeted compounds (Table 6).

Melatonin, the reference ligand, showed the highest binding affinity (−6.3 kcal/mol) while fully complying with Lipinski's criteria. Notably, α-terpineol and caryophyllene exhibited comparable binding affinities despite their simpler structures. Collectively, these findings suggest that the identified phytochemicals possess favourable drug-like characteristics and may serve as promising lead compounds for MT_1-targeted interventions in sleep-related disorders. This finding was in agreement with previous study. [26] The pharmacokinetic prediction showed that α-terpineol most closely resembled the standard drug, melatonin, with high gastrointestinal absorption, blood–brain barrier (BBB) permeability, and no predicted inhibition of major CYP450 enzymes, indicating favourable oral bioavailability and a low potential for drug–drug interactions (Table 7). Although its binding affinity (−5.8 kcal/mol) was slightly lower than that of melatonin (−6.3 kcal/mol), its overall ADME profile was highly comparable. By contrast, caryophyllene, *p*-cymene, and naphthalene exhibited lower gastrointestinal absorption than melatonin. While *p*-cymene and naphthalene were predicted to cross the BBB, caryophyllene lacked BBB permeability and showed inhibition of CYP2C19 and CYP2C9. Similarly, *p*-cymene and naphthalene inhibited CYP3A4 and CYP1A2, respectively, suggesting a greater potential for metabolic interactions than the standard drug. Above all, α-terpineol demonstrated the most favourable pharmacokinetic profile among the identified phytochemicals, highlighting its potential as a promising MT_1-targeted lead compound for sleep-related disorders. This observation is in accordance with the previous report. [27,28]

The toxicity prediction revealed marked differences among the identified phytochemicals when compared with the standard drug, melatonin. α-Terpineol exhibited the most favourable safety profile, showing no predicted cytotoxicity, carcinogenicity, or immunotoxicity, with a high LD_{50} value (2830 mg/kg; toxicity class 5), indicating relatively low acute toxicity. Caryophyllene also demonstrated low acute toxicity (LD_{50} = 5300 mg/kg; class 5) and lacked predicted cytotoxicity and carcinogenicity, although it was identified as potentially immunotoxin (Table 8). In contrast, *p*-cymene and naphthalene showed less favourable toxicity profiles. Both were predicted to be carcinogenic, while *p*-cymene exhibited the highest predicted acute toxicity (LD_{50} = 3 mg/kg; class I), suggesting a substantial safety concern. Naphthalene displayed moderate acute toxicity (LD_{50} = 316 mg/kg; class 4), comparable to melatonin (LD_{50} = 963 mg/kg; class 4), but its predicted carcinogenicity may limit its therapeutic potential. Collectively, α-terpineol demonstrated a more favourable toxicity profile than melatonin, whereas caryophyllene showed low acute toxicity with some immunotoxin liability. These findings identify α-terpineol as the safest candidate among the investigated phytochemicals and support its further evaluation as a potential MT_1-targeted agent for sleep-related disorders. This study was in support of previous report. [29]

Conclusion

The essential oil of *Monodora myristica* dried seeds contains bioactive phytochemicals with promising MT_1 receptor-binding properties. Among the identified compounds, α-terpineol emerged as the most promising lead candidate, exhibiting receptor affinity comparable to melatonin, favorable drug-like properties, optimal pharmacokinetics, and a low predicted toxicity profile. These findings highlight α-terpineol as a potential natural MT_1 modulator for the management of sleep-related disorders. However, further *in vitro*, *in vivo*, molecular dynamics, and clinical studies are required to validate its efficacy, safety, and therapeutic potential.

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