



Review Article

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Deciphering the Evolutionary Dynamics of Fish and Human Melatonin Receptors with Pineal Peptides Through a Bioinformatics Approach

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Abstract

Melatonin Receptor Proteins (MRPs) are G-protein-coupled receptors that regulate reproduction, immune function, and bone metabolism across vertebrates, including fish. Using an integrated bioinformatics pipeline, we modelled, docked, and simulated the human melatonin receptors MT1A and MT1B and the fish (*Labeo rohita*) receptors Mel1a, Mel1b, and Mel1c in complex with the synthetic pineal tetrapeptide epitalon. Subcellular localisation predictions placed all five receptors predominantly at the inner plasma membrane. Ramachandran plot analysis confirmed high-quality homology models, with 91.5–94.1% of residues in favoured regions across the receptors (94.1% for fish Mel1b and 91.5% for human MT1A). Molecular docking with AutoDock Vina yielded binding energies of –7.50 and –6.30 kcal/mol for MT1A and MT1B, and –7.4, –6.3, and –7.2 kcal/mol for Mel1a, Mel1b, and Mel1c, respectively. Epitalon engaged the receptor active sites through hydrogen bonding, involving residues such as ASN162, THR178, TYR285, GLN181, and ASN255 in MT1A, and ASN189, GLY131, GLY135, ASN282, TRP278, THR205, and GLN208 in Mel1a. A 10 ns molecular dynamics simulation of each receptor–epitalon complex showed that four of the five receptors remained conformationally stable, whereas fish Mel1c displayed markedly higher RMSD, RMSE, and radius-of-gyration values, indicating greater structural flexibility and reduced complex stability. Together, these findings characterise the structural basis of epitalon binding to melatonin receptors and provide a foundation for designing receptor-targeted therapies for reproductive disorders in fish and for metabolic and circadian disorders in humans.

Keywords: Epitalon, Fish, Human, Melatonin receptor, Molecular docking, Molecular dynamics

Introduction

The pineal gland, also known as the epiphysis cerebri, is a neuroendocrine structure in the epithalamus comprising pinealocytes, interstitial cells, perivascular phagocytes, pineal neurons, and peptidergic neuron-like cells, of which the pinealocytes secrete mela-

tonin [3]. Melatonin (N-acetyl-5-methoxytryptamine), first isolated from bovine pineal gland by Aaron B. Lerner in 1958 [3,39], is among the most evolutionarily conserved neurohormones and acts as a signalling molecule in tissues ranging from the retina and hip-

pocampus [6,9,29] to the gonads [7,8,17], cardiovascular system [27], liver and kidney [14], skin [34] and immune cells [38,39]. Through these actions, melatonin regulates circadian rhythm — including disruptions such as jet lag and shift-work disorders — sleep, and immune function [16,17], as well as reproduction and antioxidant defence [12].

Comparative analysis of melatonin signalling across vertebrates offers insight into the adaptive strategies that accompanied the transition from aquatic to terrestrial life. In humans, melatonin acts via the retino-hypothalamic tract on two G-protein-coupled receptors, MT1 and MT2 [1]. Fish possess a more elaborate melatonin system, reflecting the pineal gland's direct photosensitivity and an additional, lunar-light-sensitive receptor subtype, Mel1c, that has also been reported in amphibians [20,26,30,31].

Beyond melatonin, the pineal gland also secretes a family of pineal peptides that regulate circadian rhythm, immune response, and reproductive health [15]. Epithalamin, a bovine pineal extract, exerts gero-protective effects by normalising pineal function in ageing models [21], and sequence analysis of this extract led to the synthesis of epitalon, a tetrapeptide (Ala-Glu-Asp-Gly, AEDG) that retains the bioactivity of epithalamin in a form small enough to cross cellular and nuclear membranes efficiently [21]. Epithalamin extends lifespan in rodents by slowing the ageing of the reproductive and immune systems and by enhancing antioxidant capacity [4,5], effects partly attributed to its capacity to increase melatonin

synthesis and secretion [11]. Consistent with this mechanistic link, melatonin and epithalamin produce comparable effects on lifespan, lipid peroxidation, and the activity of antioxidant enzymes such as superoxide dismutase and catalase [42].

Despite this mechanistic overlap, the structural basis of pineal-peptide interaction with melatonin receptors remains poorly characterised, particularly across species that diverged early in vertebrate evolution. In the present study, melatonin receptor and pineal peptide sequences were retrieved from UniProt and PubChem, and structural modelling [43,44], molecular docking, and molecular dynamics simulation [10,13] were used to characterise the interaction of epitalon with the human receptors MT1A and MT1B and the fish receptors Mel1a, Mel1b, and Mel1c. By comparing receptor structure, binding-site architecture, and complex stability across species, this in-silico study establishes a structural framework for future therapeutic and experimental work on metabolic and circadian pathologies.

Methodology

Identification and Protein Sequence Retrieval

UniProt (<https://www.uniprot.org/>) is a freely available, open-access resource that provides programmatic access to curated protein knowledge [2]. Figure 1 summarises the overall workflow of the study, and Table 1 lists the bioinformatics tools and databases used.

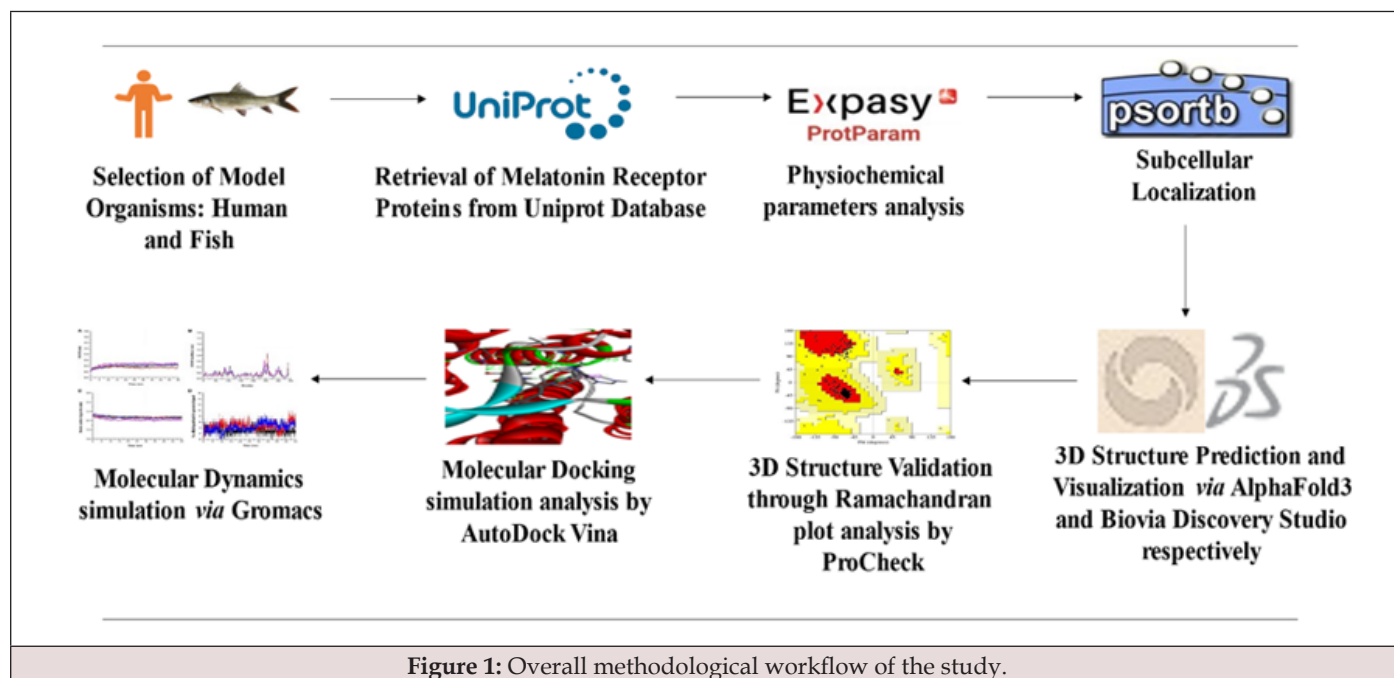


Figure 1: Overall methodological workflow of the study.

Table 1: Software and databases used in the study.

S. No.	Software/Database	Link
1	UniProt	https://www.uniprot.org/
2	ProtParam	https://web.expasy.org/protparam/
3	PSORTb	http://www.psort.org/psortb
4	AlphaFold 3	https://alphafoldserver.com/
5	BIOVIA Discovery Studio (BDS)	https://discover.3ds.com/discovery-studio-visualizer-download
6	PROCHECK	https://www.ebi.ac.uk/thorntonsrv/software/PROCHECK/
7	PubChem	https://pubchem.ncbi.nlm.nih.gov/
8	AutoDock Vina	http://autodock.scripps.edu/resources/raccoon
9	GROMACS via WebGro	https://webgro.uams.edu/ProteinInWater/index.html

Proteomic Analysis

The physicochemical properties of all melatonin receptor proteins such as theoretical pI, molecular weight, number of negatively and positively charged residues, grand average of hydropathy (GRAVY), instability index, and aliphatic index were computed using the ProtParam server (<https://web.expasy.org/protparam/>).

Subcellular Localization of Proteins

Subcellular localisation was predicted for each receptor using PSORTb (<http://www.psort.org/psortb>; [45]), which classifies proteins as extracellular, outer membrane, periplasmic, inner membrane, or cytoplasmic information relevant to predicting receptor function and drug accessibility.

Structure Prediction and Visualization

Three-dimensional structures of the melatonin receptors were predicted from their amino acid sequences using AlphaFold 3 (<https://alphafoldserver.com/>; [22]), a template-based (homology) modelling approach, and visualised using BIOVIA Discovery Studio (BDS) Visualizer (<https://discover.3ds.com/discovery-studio-visualizer-download>; [40]).

Structure Validation

Model quality was assessed by Ramachandran plot analysis in PROCHECK (<https://www.ebi.ac.uk/thorntonsrv/software/PROCHECK/>; [23]), examining the proportion of residues in favoured and allowed regions, the distribution of glycine and proline residues, and the phi/psi dihedral angles and backbone conformation of each model.

Table 2: Accession ID, sequence length, and receptor type of the melatonin receptor proteins used in this study.

S. No.	Accession ID	Sequence length	Receptor type	Organism
1	P48039	362 aa	MT1A	<i>Homo sapiens</i>
2	P49286	350 aa	MT1B	<i>Homo sapiens</i>
3	A0A6P8M1G9	344 aa	Mel1a	<i>Labeo rohita</i>
4	A0A6P8MAC0	297 aa	Mel1b	<i>Labeo rohita</i>
5	A0A498NF27	442 aa	Mel1c	<i>Labeo rohita</i>

Molecular Docking Simulation Analysis

Epitalon was retrieved from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) in SDF format [33] and converted to PDB format using PyMOL. Docking of epitalon against each melatonin receptor was performed using AutoDock Vina. (<http://autodock.scripps.edu/resources/raccoon>; [13]).

Molecular Dynamics Simulation

For each receptor, the docking pose with the lowest binding energy was selected for further analysis. Following system neutralisation, a 10 ns molecular dynamics simulation with periodic boundary conditions (500,000 steps) was performed for each receptor–ligand complex using GROMACS. Trajectories were analysed for root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and radius of gyration (ROG) [41] to characterise the kinetic and thermodynamic stability of each complex.

Results and Discussion

Retrieved Protein Sequence Analysis

Melatonin receptor sequences for human MT1A and MT1B and for *Labeo rohita* Mel1a, Mel1b, and Mel1c were retrieved from UniProt in FASTA format (Table 2) and used as input for structure prediction, docking, and molecular dynamics simulation. Both species possess MT1 and MT2 orthologues, but fish additionally express Mel1c [24], whose signalling pathway may be more complex than in mammals [35–37]; differences in the melatonin-synthesising enzyme arylalkylamine N-acetyltransferase (AANAT) further reflect this divergence between fish and humans [18,19].

Analysis of Physicochemical Characteristics

Physicochemical analysis of the five receptors (Table 3) showed molecular weights ranging from 33,695.81 Da (LMel1b) to 49,064.78 Da (LMel1c), with theoretical pI values above 7 for all receptors. Instability indices ranged from 32.42 to 48.96 — lower values denoting greater stability — while aliphatic indices, which correlate positively with thermal stability, ranged from 114.41 to 120.80.

GRAVY values ranged from 0.543 (MT1B) to 0.674 (LMel1b); lower GRAVY values indicate more favourable interaction with the aqueous environment (Wang, *et al.*, 2021). Molecular weight and other physicochemical properties are relevant to drug-target selection, as proteins near the optimal molecular weight for drug development (~110 kDa) are generally easier to purify and remain functionally stable across a wider range of conditions (Naz, *et al.*, 2015).

Table 3: Physicochemical properties of the melatonin receptors in human and fish.

Receptor	No. of AA	Theoretical pI	MW (Da)	Negative residues	Positive residues	Instability index	Aliphatic index	GRAVY
LMel1a	344	9.42	38991.24	17	32	32.42	118.92	0.583
LMel1b	297	9.39	33695.81	14	24	37.44	114.41	0.674
LMel1c	442	9.14	49064.78	20	33	35.94	115.97	0.653
HMT1A	350	9.55	39374.76	14	31	33.58	120.8	0.609
HMT1B	362	9.12	40188.39	17	28	48.96	115.06	0.543

Localization of Melatonin Receptor Proteins

Subcellular localisation predictions (Figure 2) placed most melatonin receptor proteins at the inner membrane (~90%), with the remainder distributed across the cytoplasm, periplasm, outer

membrane, and extracellular compartments. Because subcellular localisation is central to understanding protein activity, trafficking, and drug accessibility [25,26,37], the predominance of inner-membrane localisation supports the pharmacological relevance of these receptors as therapeutic targets.

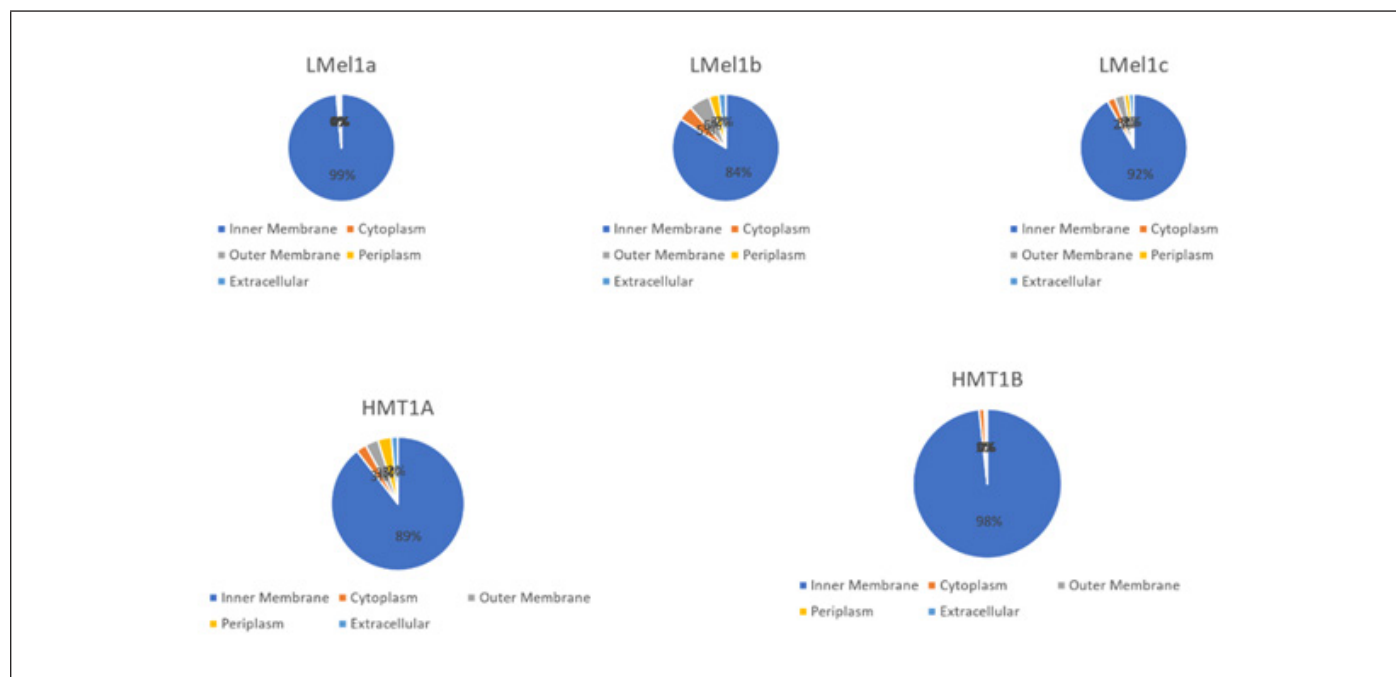


Figure 2: Subcellular localisation of melatonin receptor proteins in fish and humans. Most proteins were localised to the inner membrane (~90%). "L" and "H" denote *Labeo* and human receptors, respectively.

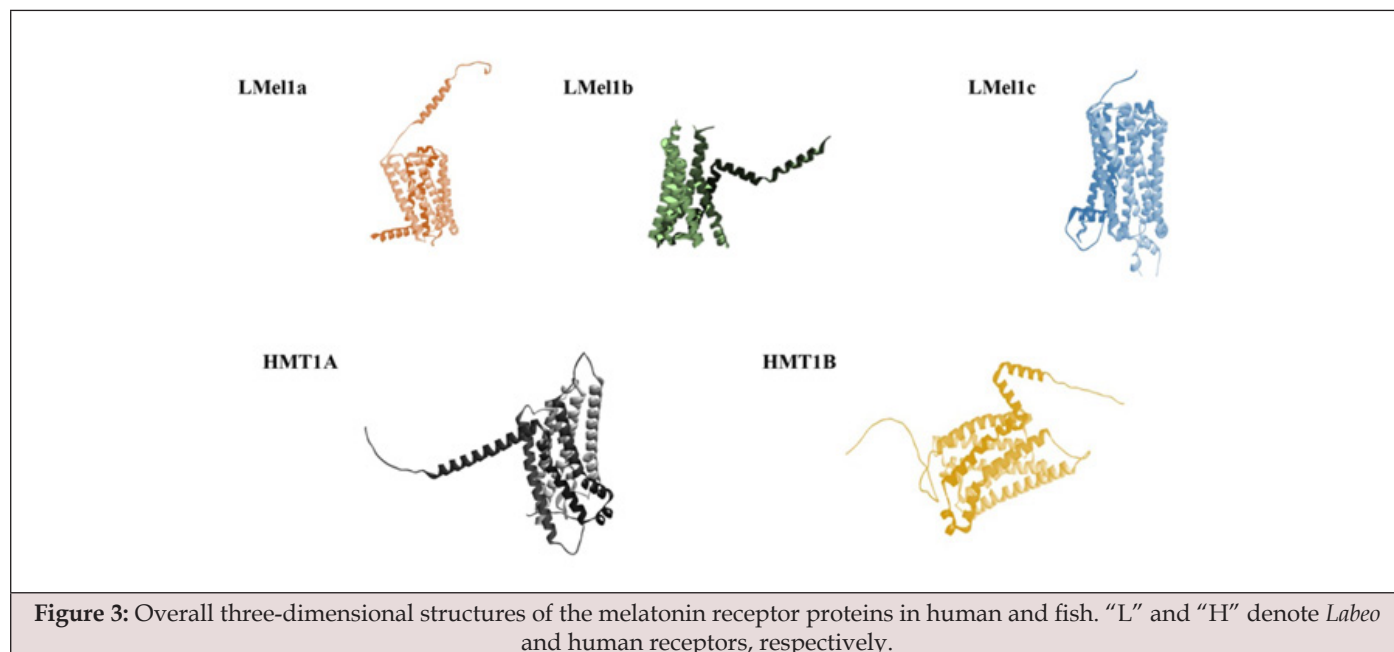
Homology Modelling and Structure Prediction

Structural models of all five receptors displayed the canonical seven-transmembrane-helix architecture characteristic of the GPCR family (Figure 3), predicted using AlphaFold 3 [22] and visualised

in BIOVIA Discovery Studio. Surface analysis revealed a comparatively low-hydrophobicity binding pocket in the human receptors that favours ligand binding, with the MT1 and MT2 loop regions contributing to ligand selectivity and receptor activation [30-32]. Fish receptor surfaces were structurally more diverse; the larger,

more exposed binding site of Mel1c, for example, may allow it to accommodate a broader range of ligands [28,29]. These structural differences inform both GPCR-targeted drug design and our under-

standing of the evolutionary divergence of melatonin receptors between fish and humans.



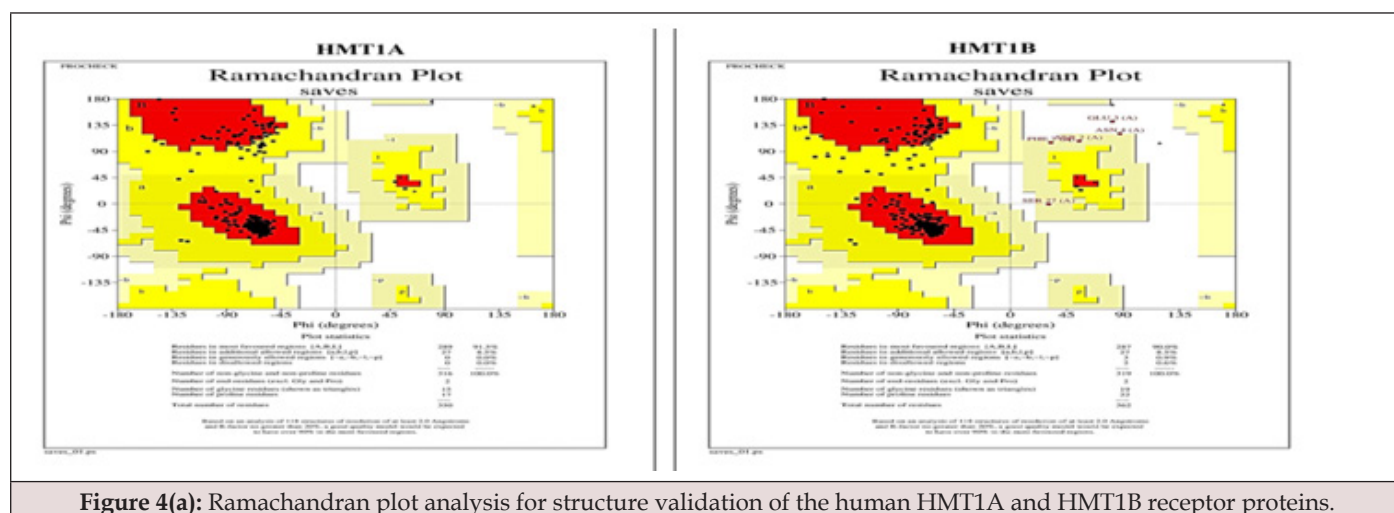
Structure Validation of Melatonin Receptors

Model quality was assessed by Ramachandran plot analysis prior to docking, with residues in the most favoured regions shown in red and those in disallowed regions in white; models with more than 90% of residues in favoured regions were considered suitable for docking.

Ramachandran plot analysis for structure validation in hu-

mans:

For the human receptors (Figure 4a), 91.5% and 90% of residues occupied the most favoured regions of MT1A and MT1B, respectively, with only 0.0% and 0.6% of residues in disallowed regions; most dihedral angles clustered within the stereochemically stable alpha-helical regions typical of GPCRs. Both models were therefore considered suitable for molecular docking.



Ramachandran plot analysis for structure validation in fish:

For the fish receptors (Figure 4b), 92.5%, 94.1%, and 94.0%

of residues fell within the most favoured regions of Mel1a, Mel1b, and Mel1c, respectively, with 0.0%, 0.4%, and 0.0% of residues in disallowed regions. All three models met the quality threshold for docking studies.

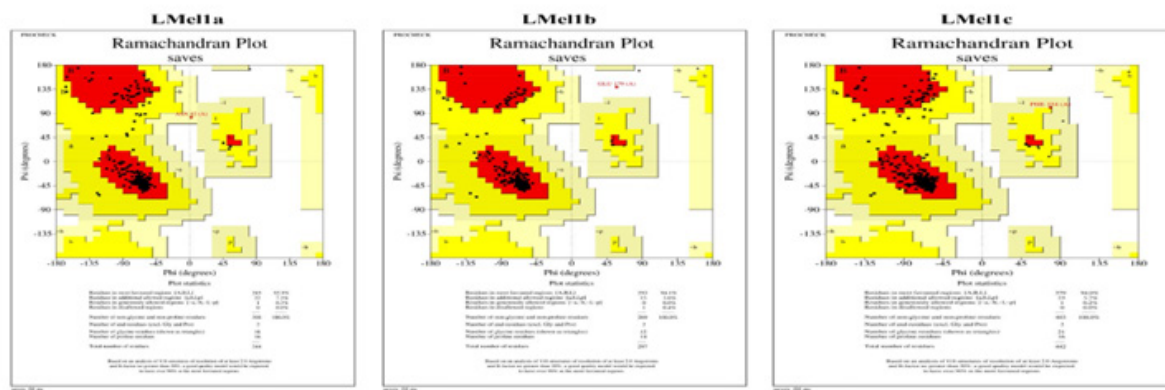


Figure 4(b): Ramachandran plot analysis for structure validation of the fish LMel1a, LMel1b, and LMel1c receptor proteins.

Molecular Docking Simulation and Intermolecular Interaction Analysis

Molecular docking is a widely used approach for virtual screening of candidate ligands. Docking of epitalon against the human receptors MT1A and MT1B and the fish receptors Mel1a, Mel1b, and Mel1c using AutoDock Vina yielded binding energies of -7.50 and -6.30 kcal/mol for MT1A and MT1B, and -7.4, -6.3, and -7.2 kcal/mol for Mel1a, Mel1b, and Mel1c, respectively, indicating favourable and broadly conserved binding across species.

Evaluation of ligand-protein binding affinities and residue interactions in humans:

Molecular interactions between epitalon and the human melatonin receptors were analysed using BIOVIA Discovery Studio Visualizer. Epitalon formed five hydrogen bonds with the active-site residues ASN162, THR178, TYR285, GLN181, and ASN255 in MT1A, and with ILE161, TYR152, THR157, ARG248, ARG138, and GLY75 in MT1B (Figure 5a, b).

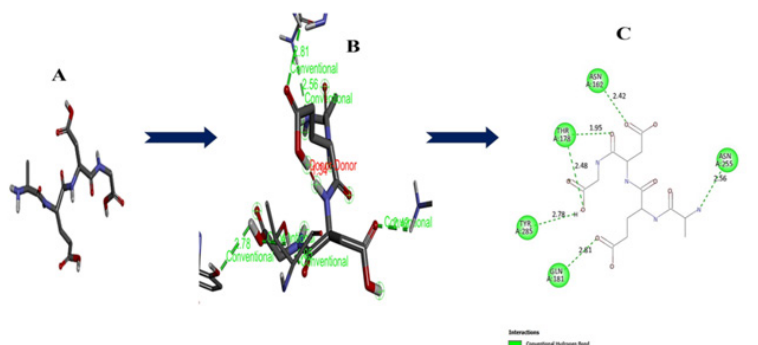


Figure 5(a): Molecular interactions between the melatonin receptor protein and the epitalon ligand, showing the most favourable binding energy of -7.50 kcal/mol. (A) Three-dimensional structure of epitalon. (B) HMT1A docked with epitalon. (C) Two-dimensional ligand-protein interaction diagram.

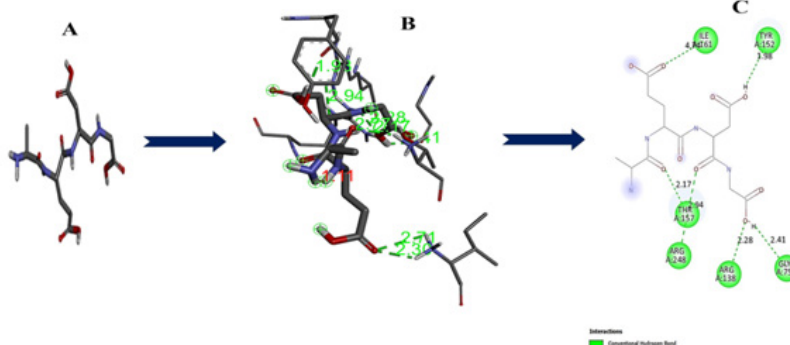


Figure 5(b): Molecular interactions between the melatonin receptor protein and the epitalon ligand, showing the most favourable binding energy of -6.30 kcal/mol. (A) Three-dimensional structure of epitalon. (B) HMT1B docked with epitalon. (C) Two-dimensional ligand-protein interaction diagram.

Evaluation of ligand–protein binding affinities and residue interactions in fish

In the fish receptors, epitalon engaged ASN189, GLY131,

GLY135, ASN282, TRP278, THR205, and GLN208 in Mel1a; GLU259, PRO7, SER9, LEU8, and ASN253 in Mel1b; and VAL196, PHE183, ASN257, and TYR191, among more than twenty residues, in Mel1c (Figure 6a–c).

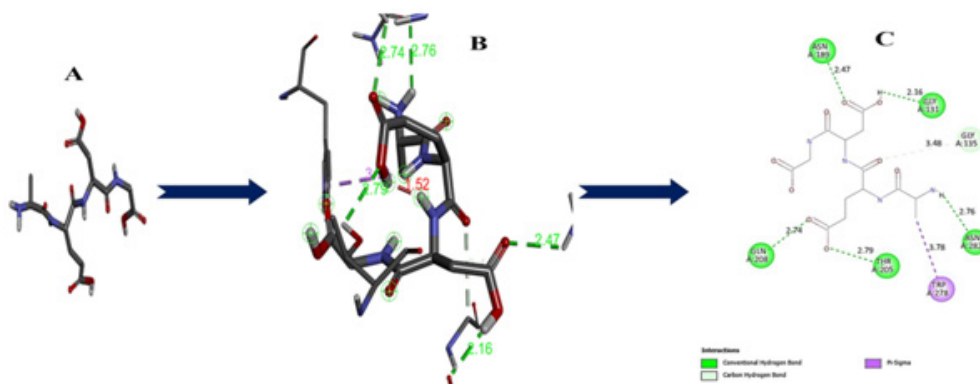


Figure 6(a): Molecular interactions between the melatonin receptor protein and the epitalon ligand, showing the most favourable binding energy of -7.4 kcal/mol. (A) Three-dimensional structure of epitalon. (B) LMel1a docked with epitalon. (C) Two-dimensional ligand–protein interaction diagram.

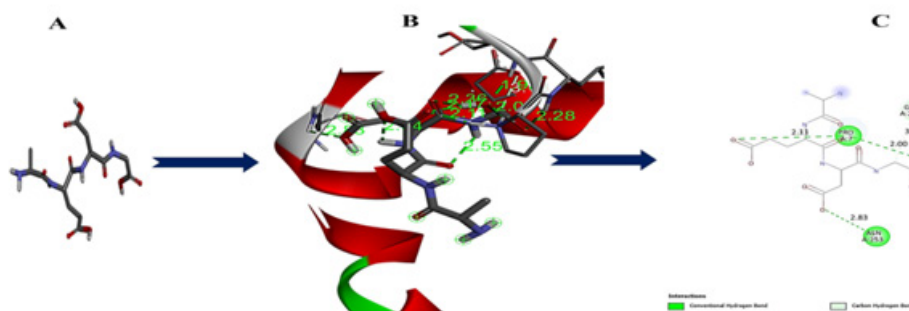


Figure 6(b): Molecular interactions between the melatonin receptor protein and the epitalon ligand, showing the most favourable binding energy of -6.3 kcal/mol. (A) Three-dimensional structure of epitalon. (B) LMel1b docked with epitalon. (C) Two-dimensional ligand–protein interaction diagram.

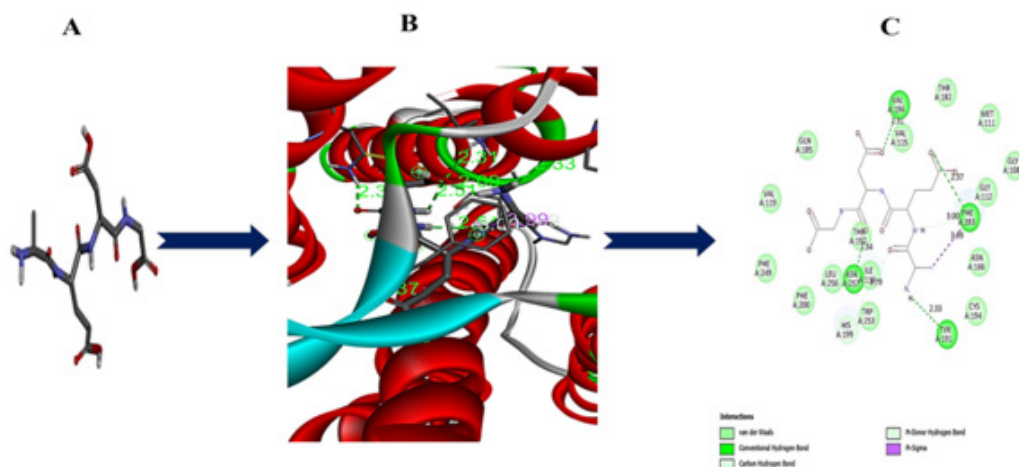


Figure 6(c): Molecular interactions between the melatonin receptor protein and the epitalon ligand, showing the most favourable binding energy of -7.2 kcal/mol. (A) Three-dimensional structure of epitalon. (B) LMel1c docked with epitalon. (C) Two-dimensional ligand–protein interaction diagram.

Molecular Dynamics Simulation Analysis

Molecular dynamics (MD) simulation is a key tool for understanding the structural and functional stability of proteins. A 10 ns MD simulation of each receptor–epitagon complex was performed, sufficient to capture side-chain reorganisation at the binding interface, and trajectories were analysed for RMSD, RMSF, and radius of

gyration (ROG).

RMSD values (Figure 7a) were 0.24 nm for both human MT1A and MT1B, and 0.3, 0.4, and 1.3 nm for fish Mel1a, Mel1b, and Mel1c, respectively. The markedly higher RMSD of Mel1c relative to the other four receptors indicates that its complex with epitagon is comparatively less stable.

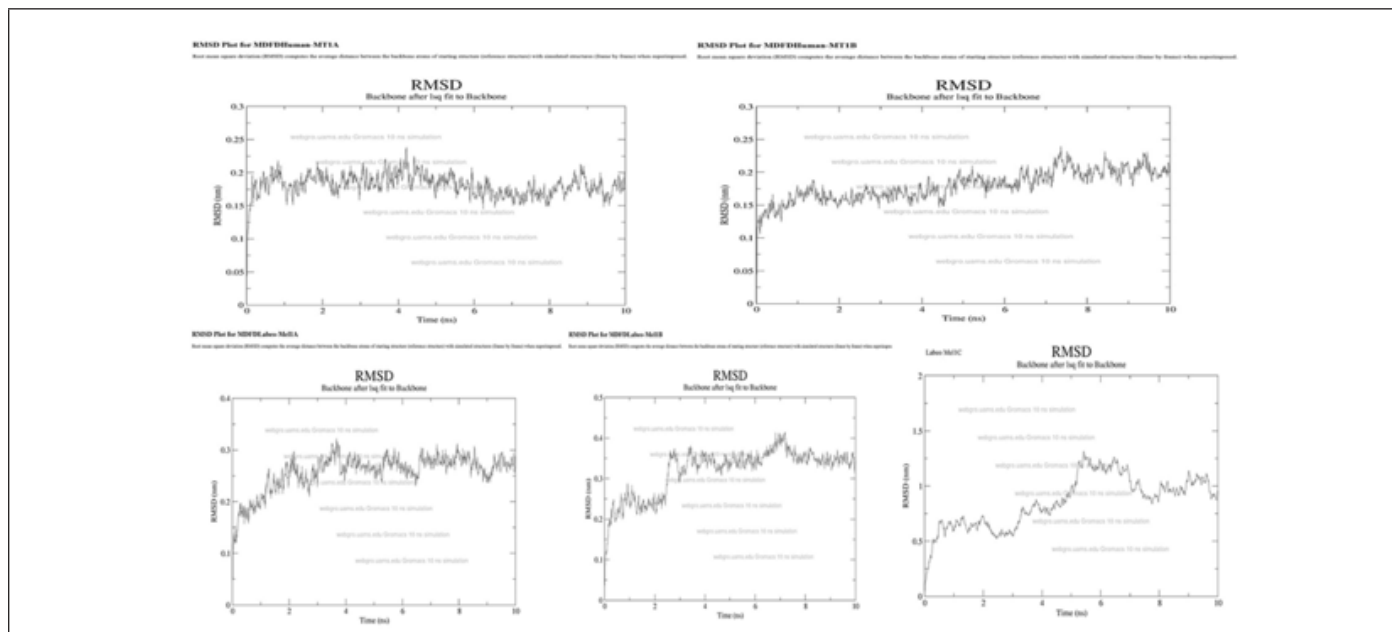


Figure 7(a): RMSD of the melatonin receptor–epitagon complexes in human and fish over the course of the 10 ns simulation.

RMSF values (Figure 7b), which reflect local residue flexibility, were higher in MT1A than in MT1B (maxima of ~0.48 nm and ~0.35 nm, respectively), with low fluctuation in the conserved transmembrane helices and higher fluctuation in the extracellular loops involved in ligand binding. Mel1a and Mel1b showed com-

parable, moderate flexibility (maxima of ~0.75 nm and ~0.65 nm, respectively), whereas Mel1c showed markedly higher flexibility (~1.9 nm), consistent with its lower conformational stability among the five receptors.

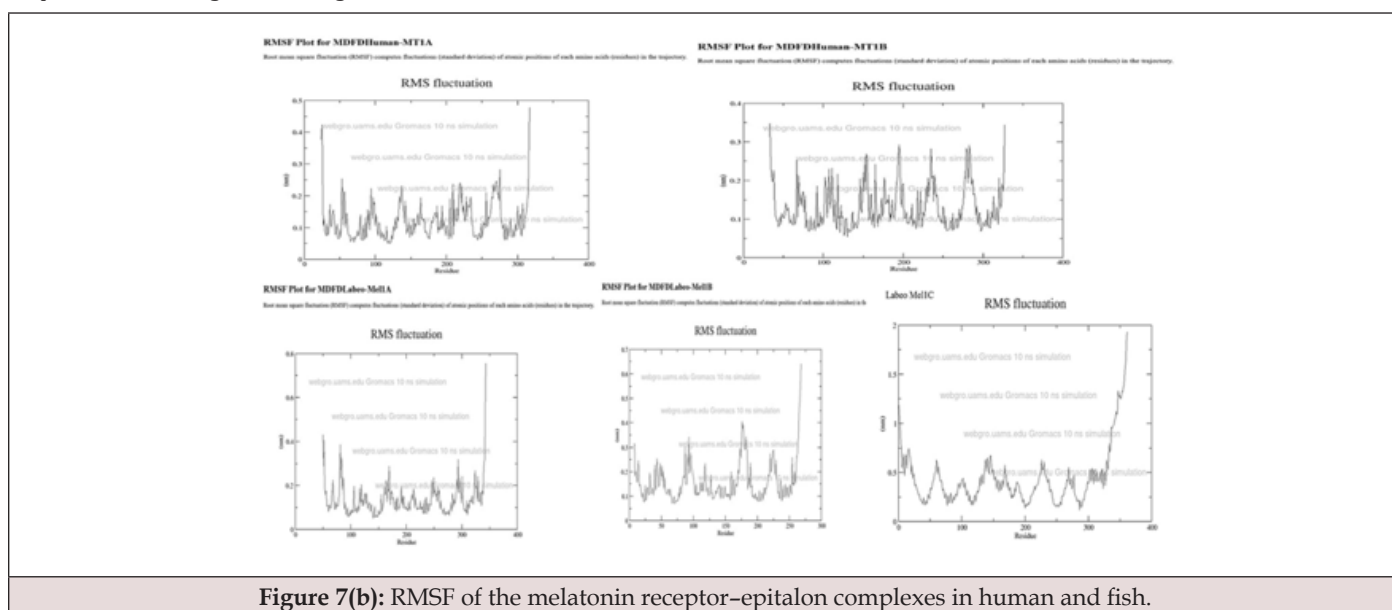


Figure 7(b): RMSF of the melatonin receptor–epitagon complexes in human and fish.

Radius of gyration (Figure 7c) indicated that human MT1A remained highly compact and rigid throughout the simulation (~2.15 nm), while MT1B showed moderate fluctuation (~2.12 nm). Among the fish receptors, Mel1a was the most compact (~2.15 nm), fol-

lowed by Mel1b (~2.0 nm), whereas Mel1c showed the largest and most variable radius of gyration (~3.08 nm), further supporting its reduced structural stability relative to the other four receptors.

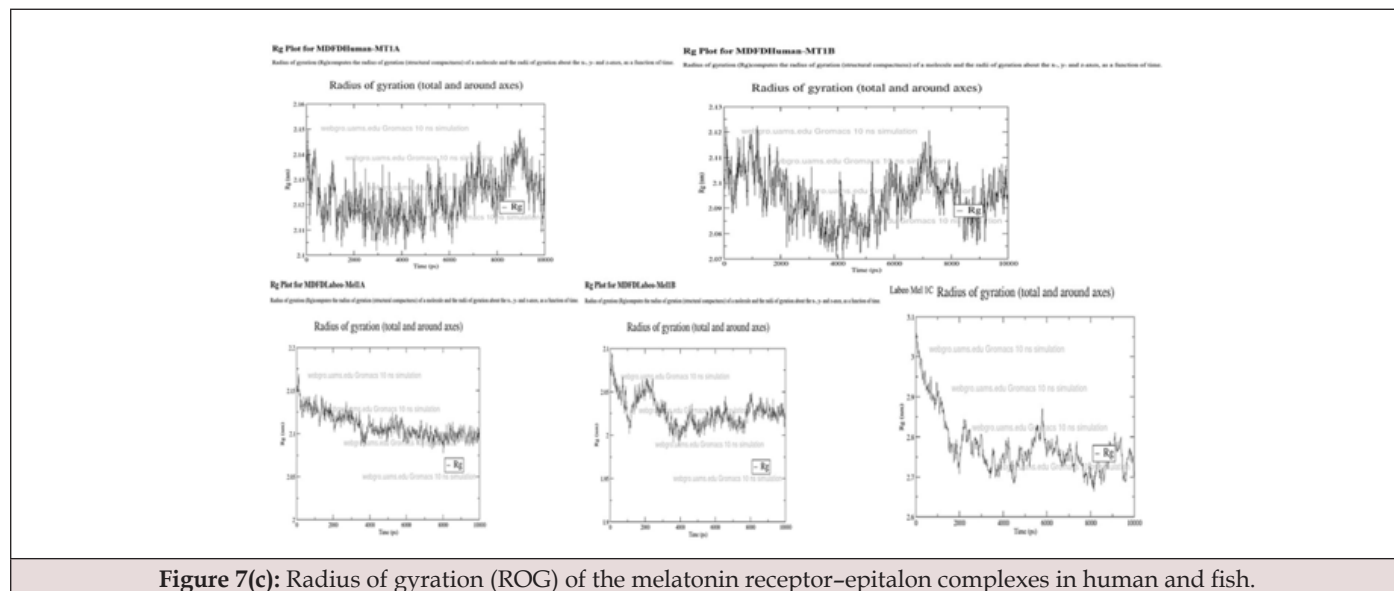


Figure 7(c): Radius of gyration (ROG) of the melatonin receptor-epitagon complexes in human and fish.

Conclusion

This study integrates homology modelling, molecular docking, and molecular dynamics simulation to characterise the structural basis of epitagon binding to melatonin receptors in humans and fish. Four of the five receptors examined, human MT1A and MT1B and fish Mel1a and Mel1b formed stable, high-affinity complexes with epitagon, whereas fish Mel1c showed comparatively lower stability, highlighting species and subtype-specific differences in receptor-ligand dynamics. These findings clarify the functional relationship of melatonin receptors across vertebrate lineages and provide a structural rationale for the design of epitagon-based or receptor-targeted therapies for reproductive disorders in fish and for metabolic and circadian disorders in humans. Extending this comparative framework to additional vertebrate classes, together with in vitro validation of the predicted binding interactions, will be an important next step in confirming the therapeutic potential identified here.

Credit Authorship Contribution Statement

Umang Verma: Writing, original draft, Investigation, Formal analysis. Ayushi Singh: Writing, review & editing. Somenath Ghosh: Supervision, Software, Methodology, Data curation, Conceptualization.

Declaration of Competing Interests

The authors declare no conflict of interest.

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