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"In silico study to identify new melatonin-like botanical cosmetic active ingredients"

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1. Introduction

Melatonin is classically considered as a chronobiological hormone regulating the circadian day-night and seasonal biorhythms. Melatonin secretion, which increases in the evening and peaks in the middle of the night, plays a crucial role in the sleep cycle. In addition, melatonin has a wide range of endocrine properties. At the skin level, melatonin exhibits potent antioxidant properties[1]. This is partially mediated by its interaction with the G-protein-coupled membrane receptors (MT-1 and MT-2).

The aim of this work is to build a reliable *in silico* model of ligand-receptor interaction, specifically with natural ligands that exhibit melatonin-like activity. This study focuses on evaluating the binding modes and affinities of several natural molecules, comparing them to those of well-characterized reference ligands, including melatonin, agomelatin, ramelteon[2], [3], [4], [5], as well as the selective MT1 inhibitor, luzindole[6], [3], [7], [8], [9], [10]. This model will be benchmarked against available experimental data on these prototypical molecules and subsequently used to screen large series of natural compounds and predict MT-1 activities.

2. Material and Methods

The human MT-1 receptor molecular model was constructed and equilibrated from the PDB 6ME5 structure [11], embedded in a lipid bilayer model. The model was subjected to molecular dynamics (MD) simulations over 1.5 μs for 3 replicas. A series of 22 botanical compounds was screened by molecular docking at two different locations: at the entrance (Figure 1a) and inside (Figure 1b) the binding pocket (Figure 1). During docking, flexibility was allowed for both the ligands and the key residues of the binding site. A subset of compounds showing strong interactions with key residues were selected for MD simulations. This allowed the dynamic behavior of the molecules inside the binding cavity to be explored, also confirming and precising the specific interactions (*i.e.,* hydrogen bonding and π–π stacking) with relevant residues.

3. Results

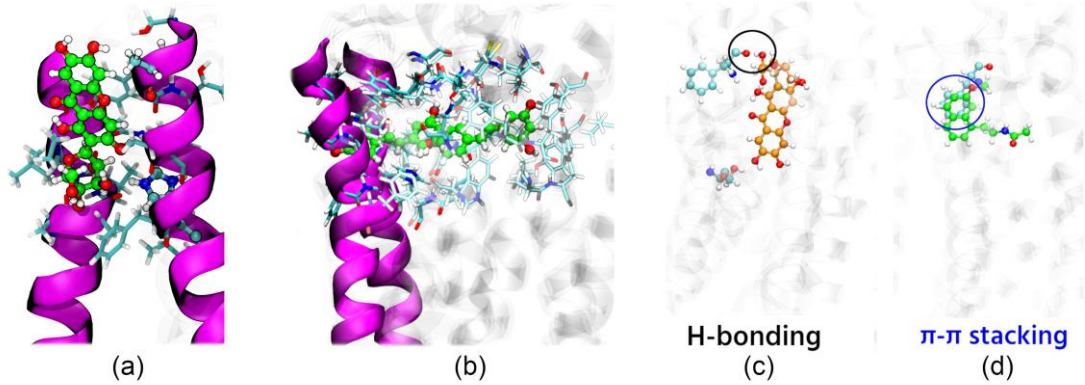

Figure 1. (a) Ligand binding at the entrance of the binding pocket; (b) ligand binding inside the binding pocket; (c) an example of a hydrogen bond interaction (black circle); (d) an example of π–π stacking interaction (blue circle). Protein structures are shown as magenta helices and light gray ribbons; ligands and key residues are represented by ball-and-stick and stick models, respectively. Hydrogen bonding and π–π stacking interactions are highlighted to illustrate key molecular interactions identified in the docking study.

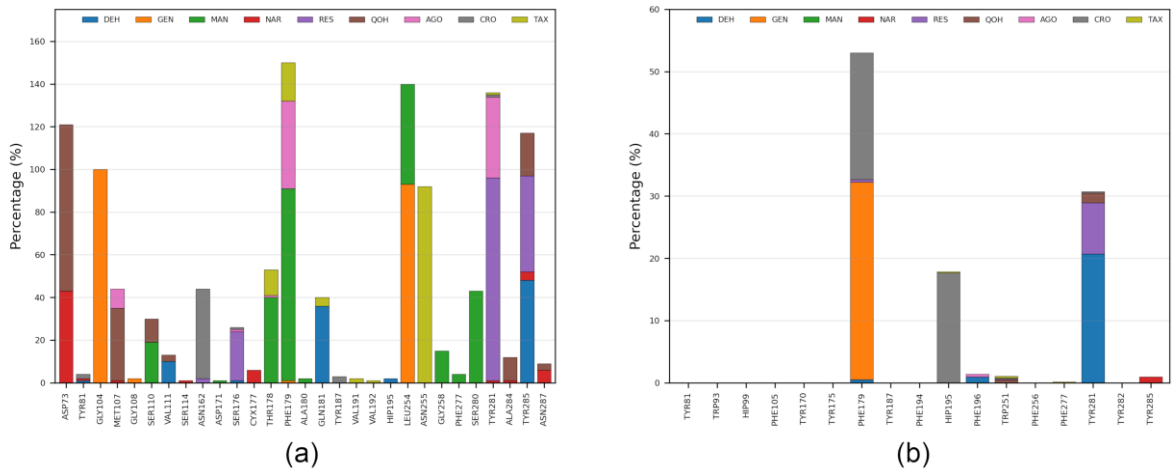

Figure 2. (a) Percentage of hydrogen bond interactions observed in docking simulations for each compound; (b) percentage of π–π stacking interactions observed in docking simulations for the same compounds. Compounds are color-coded and abbreviated as follows: DEH (blue) – dehydrosilybin; GEN (orange) – genistein; MAN (green) – mangiferin; NAR (red) – naringin; RES (purple) – resveratrol; QOH (brown) – quercetin; AGO (pink) – agomelatine; CRO (gray) – crocetin; TAX (yellow) – taxifolin.

The binding mode was elucidated, allowing a ranking according to affinities to MT-1. The docking calculations revealed a correlation between the interactions of the molecules and the

Phe179 and Asn162 key residues. Specific ligand-receptor interactions were highlighted like π-π stacking and hydrogen bonding (Figure 2, (b) and (a), respectively). The MD simulations also showed the flexibility of some molecules inside the binding pocket. We also found that melatonin and luzindole interacted more specifically with Gln181 during the simulations. The molecules were ranked according to their binding modes and structure-activity relationships were established.

4. Discussion and conclusion

MD simulations enabled the development of a reliable MT-1 receptor model, allowing the identification of natural compounds with melatonin-like activity and skin-protective effects. This model serves as a powerful tool for the virtual screening of new MT-1 activators. Future work will involve incorporating the MT-1 model into different membrane environments to better understand the influence of lipid composition on the binding cavity and ligand-protein interactions[12]. This approach opens up new opportunities for the discovery of natural compounds with therapeutic potential in skin protection and related applications.

References

[1] A. Hacışevki, B. Baba, A. Hacışevki, et B. Baba, « An Overview of Melatonin as an Antioxidant Molecule: A Biochemical Approach », in *Melatonin - Molecular Biology, Clinical and Pharmaceutical Approaches*, IntechOpen, 2018. doi: 10.5772/intechopen.79421.

[2] R. Faust *et al.*, « Mapping the melatonin receptor. 6. Melatonin agonists and antagonists derived from 6H-isoindolo[2,1-a]indoles, 5,6-dihydroindolo[2,1-a]isoquinolines, and 6,7-dihydro-5H-benzo[c]azepino[2,1-a]indoles », *J. Med. Chem.*, vol. 43, nº 6, p. 1050-1061, mars 2000, doi: 10.1021/jm980684+.

[3] C. Browning, I. Beresford, N. Fraser, et H. Giles, « Pharmacological characterization of human recombinant melatonin mt1 and MT2 receptors », *Br. J. Pharmacol.*, vol. 129, nº 5, p. 877-886, 2000, doi: 10.1038/sj.bjp.0703130.

[4] E. Cecon, A. Oishi, et R. Jockers, « Melatonin receptors: molecular pharmacology and signalling in the context of system bias », *Br. J. Pharmacol.*, vol. 175, nº 16, p. 3263-3280, août 2018, doi: 10.1111/bph.13950.

[5] L. Liu, N. Labani, E. Cecon, et R. Jockers, « Melatonin Target Proteins: Too Many or Not Enough? », *Front. Endocrinol.*, vol. 10, p. 791, nov. 2019, doi: 10.3389/fendo.2019.00791.

[6] M. L. Dubocovich, K. Yun, W. M. Al-Ghoul, S. Benloucif, et M. I. Masana, « Selective MT2 melatonin receptor antagonists block melatonin-mediated phase advances of circadian rhythms », *FASEB J.*, vol. 12, nº 12, p. 1211-1220, 1998, doi: 10.1096/fasebj.12.12.1211.

[7] V. Audinot *et al.*, « New selective ligands of human cloned melatonin MT1 and MT2 receptors », *Naunyn. Schmiedebergs Arch. Pharmacol.*, vol. 367, nº 6, p. 553-561, juin 2003, doi: 10.1007/s00210-003-0751-2.

[8] G. Spadoni *et al.*, « Towards the development of mixed MT(1)-agonist/MT(2)-antagonist melatonin receptor ligands », *ChemMedChem*, vol. 1, nº 10, p. 1099-1105, oct. 2006, doi: 10.1002/cmdc.200600133.

[9] G. Spadoni *et al.*, « Synthesis, Enantiomeric Resolution, and Structure–Activity Relationship Study of a Series of 10,11-Dihydro-5H-Dibenzo[a,d]cycloheptene MT2 Receptor Antagonists », *ChemMedChem*, vol. 2, nº 12, p. 1741-1749, 2007, doi: 10.1002/cmdc.200700141.

[10] P. Jumnongprakhon, S. Sivasinprasasn, P. Govitrapong, C. Tocharus, et J. Tocharus, « Activation of melatonin receptor (MT1/2) promotes P-gp transporter in methamphetamine-induced toxicity on primary rat brain microvascular endothelial cells », *Toxicol. Vitro Int. J. Publ. Assoc. BIBRA*, vol. 41, p. 42-48, juin 2017, doi: 10.1016/j.tiv.2017.02.010.

[11] K. Beis, « Structural basis for the mechanism of ABC transporters », *Biochem. Soc. Trans.*, vol. 43, nº 5, p. 889-893, oct. 2015, doi: 10.1042/BST20150047.

[12] J. Fantini, R. M. Epand, et F. J. Barrantes, « Cholesterol-Recognition Motifs in Membrane Proteins », *Adv. Exp. Med. Biol.*, vol. 1135, p. 3-25, 2019, doi: 10.1007/978-3-030-14265-0_1.