

Interactions of Mitragynine Pseudoindoxyl with DPPC Lipid Bilayer- A Study using Molecular Dynamics Simulations



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Abstract

Mitragynine pseudoindoxyl (MP), a derivative of mitragynine, is one of the prominent alkaloids derived from *Mitragyna speciosa*, commonly known as kratom or ketum. It exhibits considerable potential for various pharmacological applications [1]. Nevertheless, the molecular interactions between MP and cellular membranes remain poorly understood [2]. In this study, molecular dynamics (MD) simulations were employed to investigate the behavior of MP compounds within lipid bilayers, aiming to elucidate their mechanisms of membrane interaction. A model system comprising three MP molecules embedded in a fully hydrated dipalmitoylphosphatidylcholine (DPPC) lipid bilayer was simulated using the GROMACS program for a duration of 100 ns. The simulation results show that MP diffuses into the lipid bilayer region as early as ~53 ns for a single molecule and ~60 ns for a pair of MP molecules. The molecules preferentially position themselves beneath the lipid head groups. Hydrogen bonds were formed between MP and the carbonyl and phosphate groups of the lipid bilayer, as well as water molecules that entered from the aqueous region. These findings highlight the hydrophobic nature of MP, facilitating its integration into lipid bilayers. By enhancing our understanding of MP's molecular behavior and membrane interactions, this study contributes valuable insights for the development of therapeutic strategies targeting membrane-associated processes.

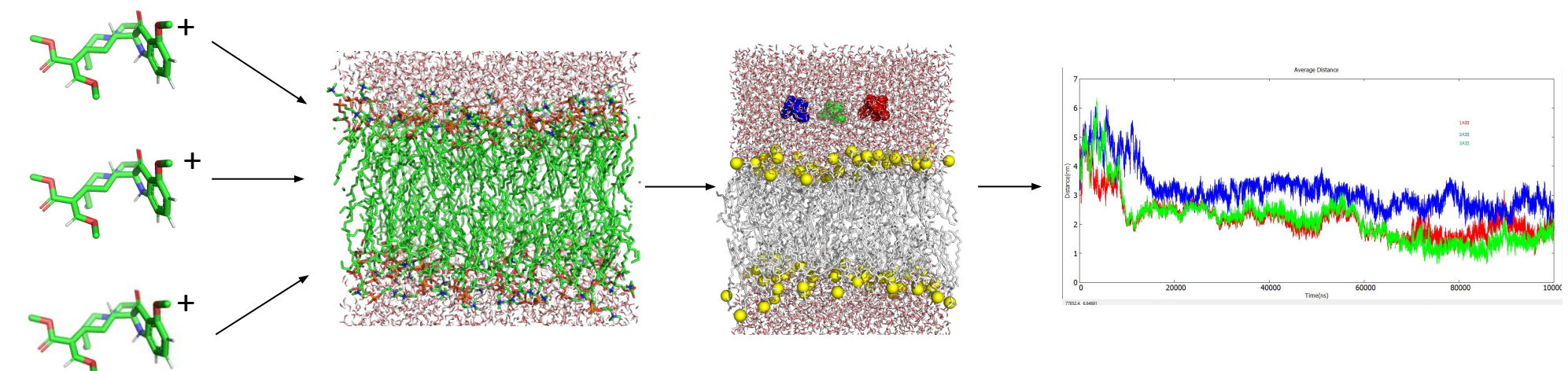
Methodology

Ligand preparation
(Automated Topology
Builder, ATB) [3]

System
preparation

MD simulation using
GROMACS 2021.5 [4]

Trajectory analysis using
Gnuplot and Xmgrace



Research Objectives

- To create a model system of protonated mitragynine pseudoindoxyl in DPPC lipid bilayer system.
- To simulate mitragynine pseudoindoxyl molecules in DPPC lipid bilayer using molecular dynamics simulations.
- To determine interactions of mitragynine pseudoindoxyl with DPPC lipid bilayer.

Result

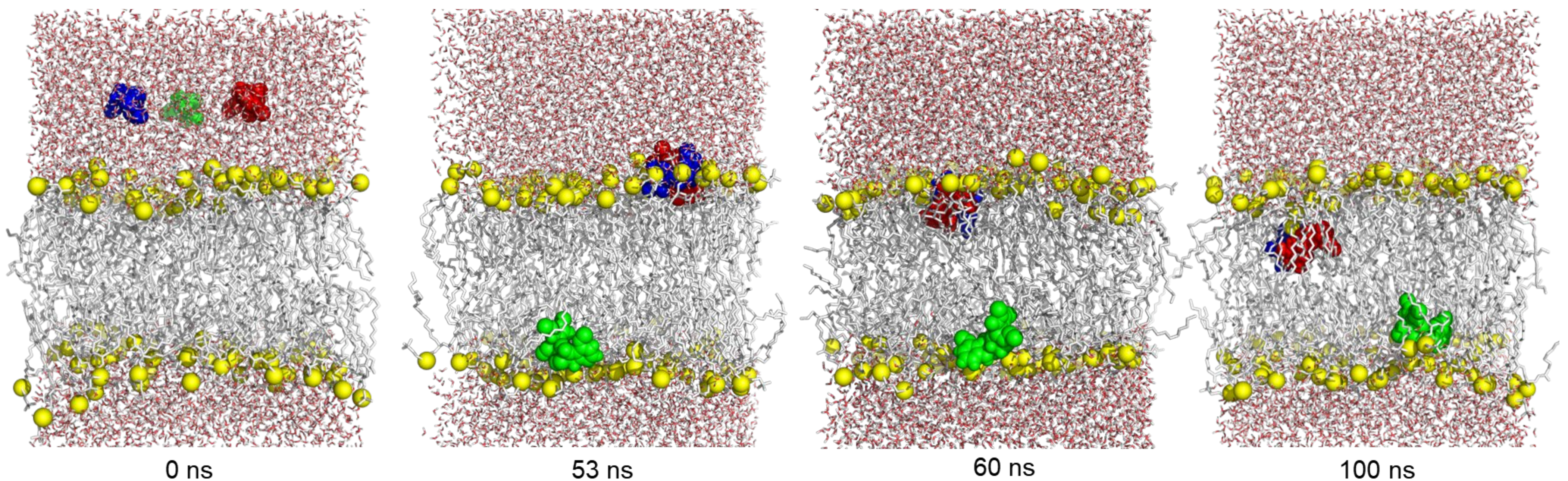


Fig 2. Interactions of three molecules of mitragynine pseudoindoxyl with lipid bilayer during the MD simulation. MP2 (green) penetrated the lipid bilayer as a single molecule, while MP1 (red) and MP3 (blue) penetrated the lipid as a pair. The compounds remain under the lipid headgroups after entering the bilayer region.

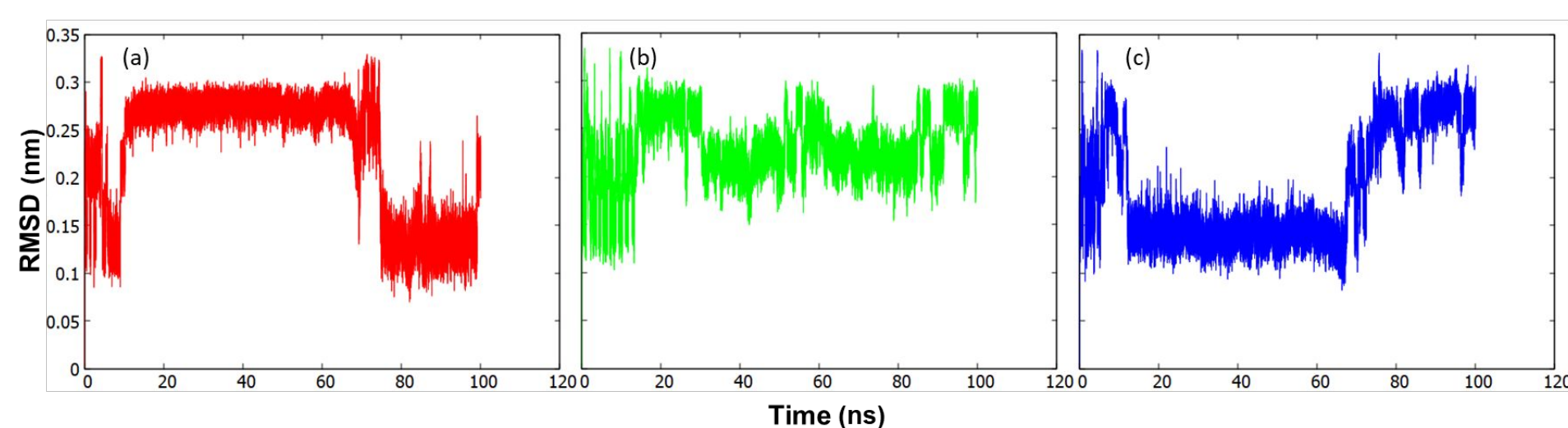


Fig 3. RMSD of each mitragynine pseudoindoxyl molecule during the simulation. MP2 (green) has the most stable RMSD during the MD simulation compared to MP1 (red) and MP3 (blue).

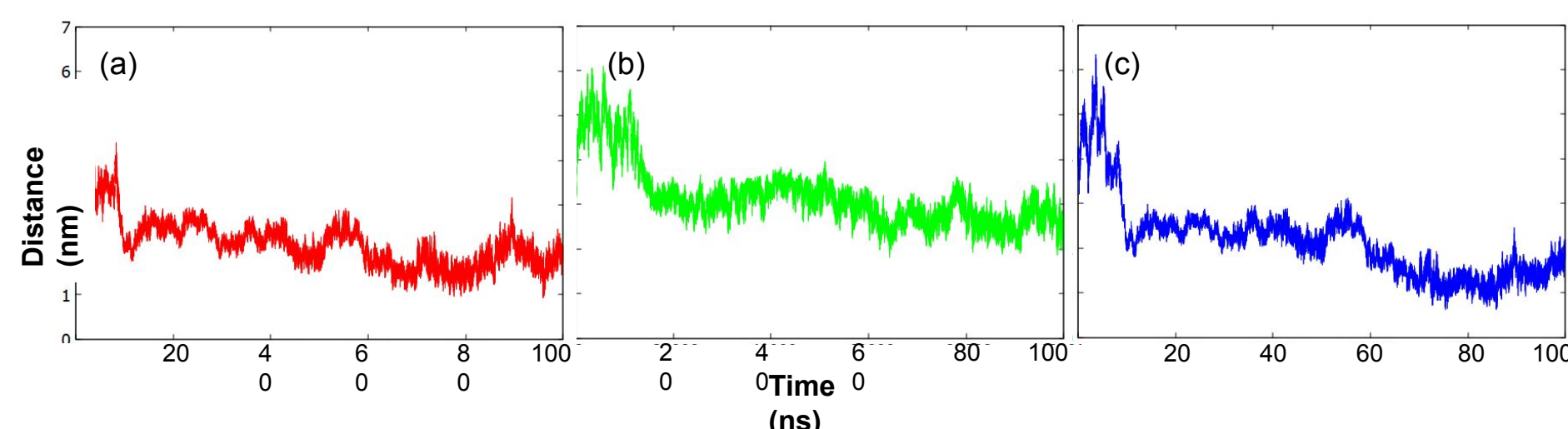


Fig 4. Average distance between the alkaloid and lipid headgroup. All the compounds start to move toward lipid headgroups in 20 ns. MP2 penetrated the lipid bilayer ~53 ns, while both MP1 and MP2 penetrated ~60 ns. The molecules positioned below the lipid headgroup in DPPC lipid bilayer.

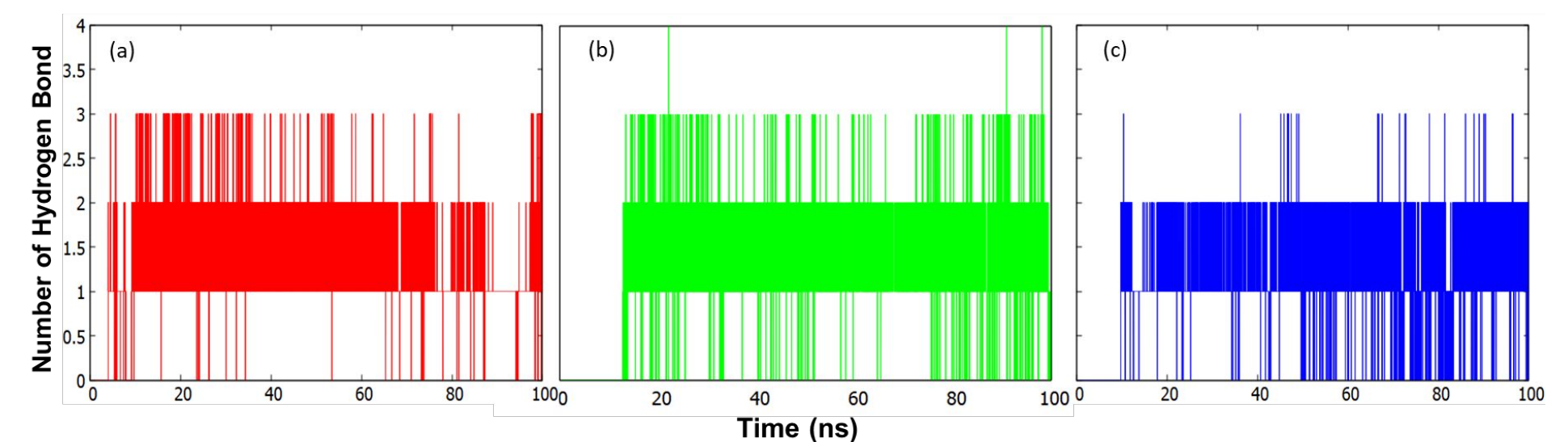


Fig 5. Hydrogen bond of each mitragynine pseudoindoxyl molecule with DPPC lipids. All MPs formed 2-3 hydrogen bonds with the DPPC lipid bilayer.

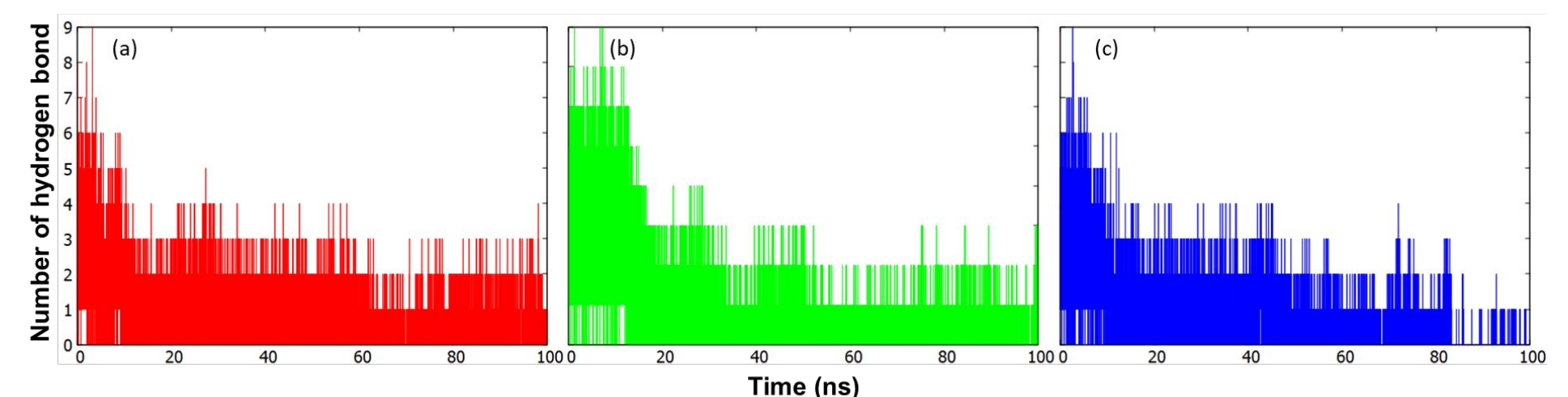


Fig 6. Hydrogen bond of each mitragynine pseudoindoxyl molecule with water. MP1, MP2, and MP3 has 1-9 hydrogen bonds during the simulation. After 20 ns, hydrogen bonding of water with MPs decreased due to their interactions with the DPPC lipid bilayer. MP2 has highest hydrogen bond with water during the early simulation.

Discussion

- A mitragynine pseudoindoxyl molecule has more hydrophobic properties which allow the molecule to penetrate the lipid bilayer.
- A single molecule of mitragynine pseudoindoxyl penetrated the DPPC lipid bilayer faster compared to a clumping of molecules. Aggregation of compounds creates a larger structure that make it more difficult to penetrate the lipid bilayer due to steric hindrance [5].
- After penetrated lipid bilayer, the MP molecules in the model system remain located at the lipid-water interphase to form hydrogen bond with carbonyl and phosphate groups of lipid as well as water molecules

Acknowledgement

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Conclusion

In conclusion, all mitragynine pseudoindoxyl able to penetrate the DPPC lipid bilayer within 53 ns to 60 ns in 100 ns MD simulation. Mitragynine pseudoindoxyl can penetrate into DPPC lipid bilayer as single compound or in pair. In the lipid bilayer, the compound positioned themselves below the lipid headgroups in order to form hydrogen bond with lipid hydrophilic constituent and water molecules

References

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