



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

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INTRODUCTION

Mitragynine, an alkaloid derived from the psychotropic plant *Mitragyna speciosa*, commonly known as kratom or ketum, is prevalent in Thailand and Malaysia. As the most abundant alkaloid present in kratom (1), mitragynine possesses significant pharmacological properties, for instance analgesic effect (2). Furthermore, Malaysia is currently revising on the Kratom's Poison Act 1952 toward legalizing kratom for medical use (3). However, despite its widespread use and potential therapeutic applications, the molecular interactions of mitragynine with cellular membranes remain poorly understood. In this study, we employed molecular dynamics (MD) simulations to investigate the behavior of mitragynine compounds interacting with membrane lipid bilayers. By elucidating the mechanism of mitragynine's interaction with lipid membranes, our research aims to shed light on its bioavailability, cellular uptake, and potential pharmacological implications. A model system comprising three mitragynine molecules embedded in a fully hydrated dipalmitoylphosphatidylcholine (DPPC) lipid bilayer was simulated using the GROMACS program for a duration of 100 ns. Our findings indicate that mitragynine rapidly diffuses into the lipid bilayer region, with penetration occurring as early as ~23 ns. During the simulation, we observed both single and paired mitragynine molecules entering the lipid bilayer, where they preferentially positioned themselves below the lipid head groups, forming hydrogen bonds with the carbonyl and phosphate groups, as well as with water molecules. Collectively, our results demonstrate the hydrophobic nature of mitragynine, enabling its interaction with and penetration into the lipid bilayer. This study contributes to a better understanding of molecular behavior of mitragynine, providing valuable insights for future drug design and development targeting cellular membranes.

OBJECTIVES

- 1.to prepare mitragynine in a DPPC lipid bilayer model system.
- 2.to simulate protonated state of mitragynine in DPPC lipid bilayer using molecular dynamics simulations.
- 3.to determine mitragynine interaction with DPPC lipid bilayer.

METHODOLOGY

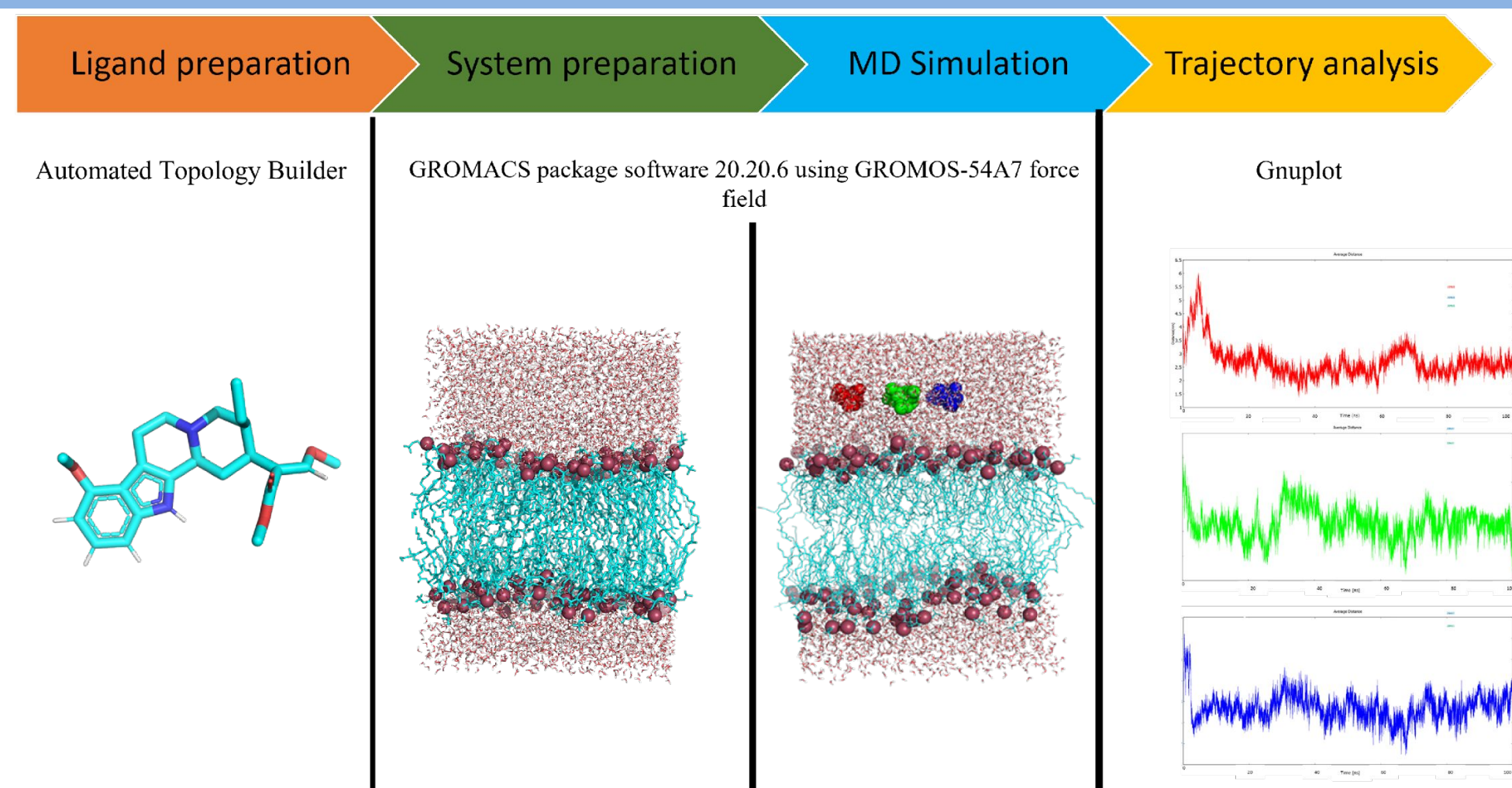


Figure 1: Methodology workflow of this study

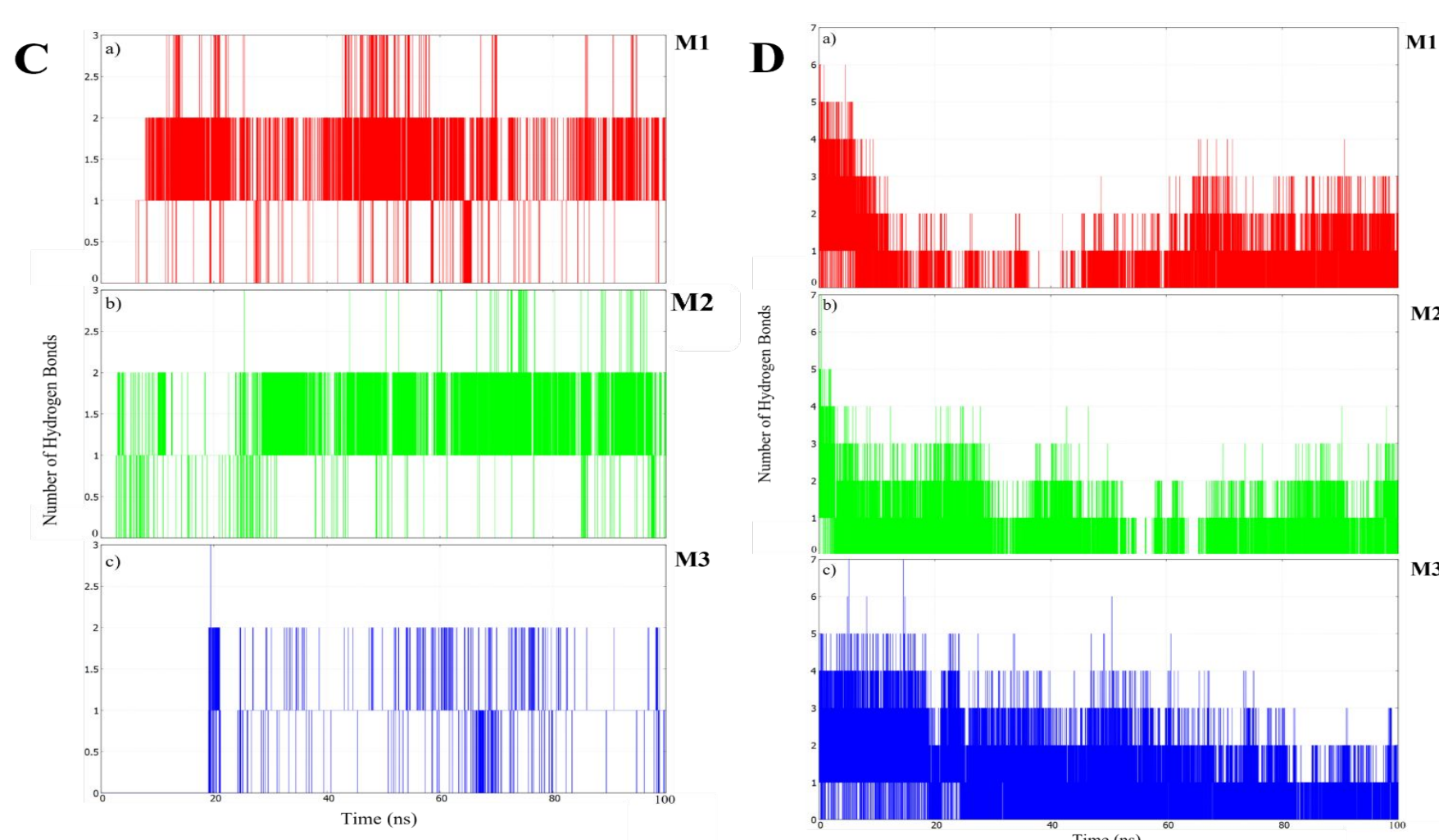


Figure 4C: Hydrogen bond interactions of mitragynine compounds with lipids. All three compounds formed 2-3 hydrogen bonds with lipids during the simulation. M3 has the least hydrogen bonds formed with the lipids.

Figure 4D: Hydrogen bond of mitragynine compounds with water molecules. All three compounds formed 2-7 hydrogen bonds with water molecules. Interaction of water molecules with mitragynines reduced when mitragynines enter the lipid bilayer.

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RESULTS

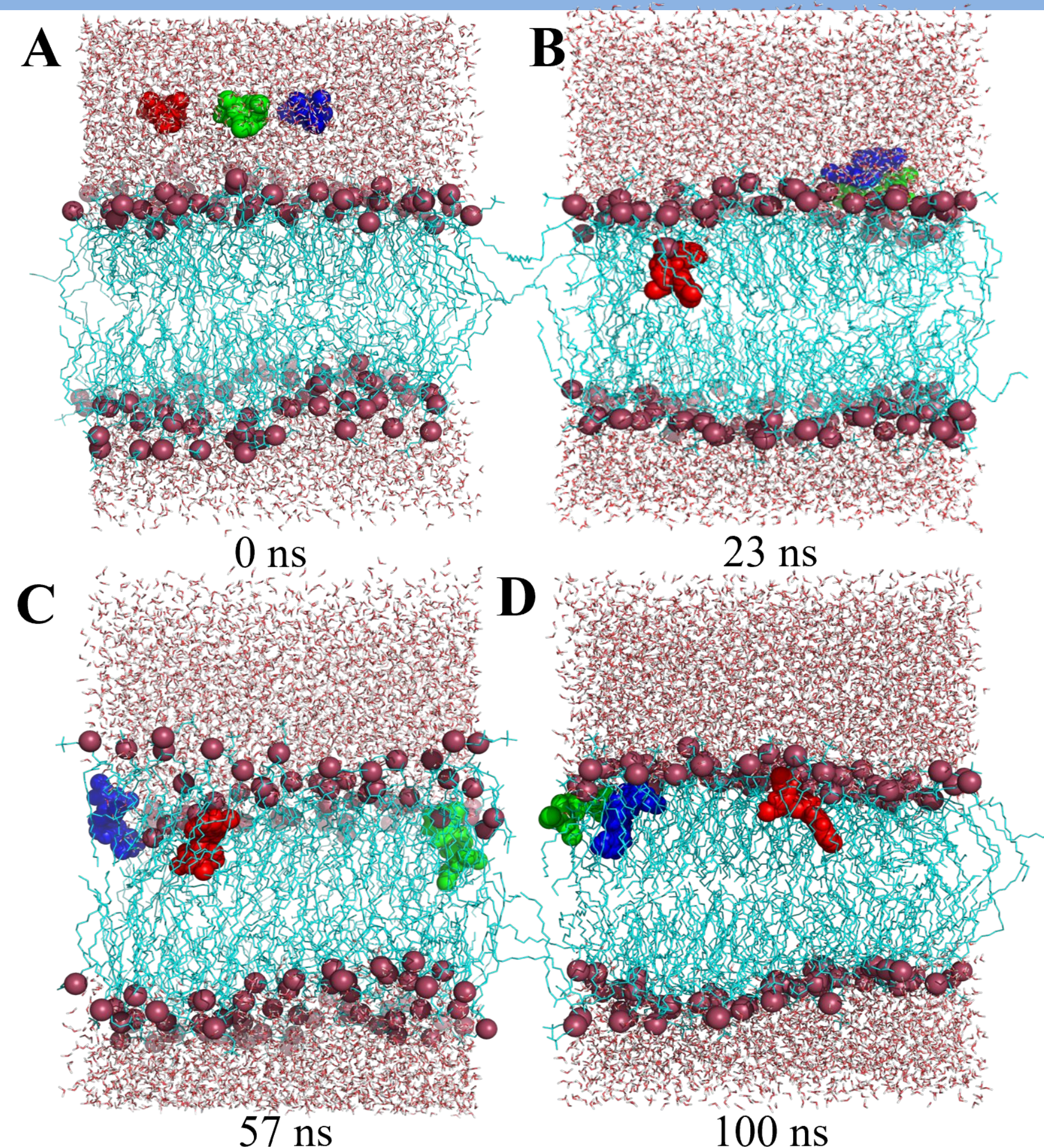


Figure 2 : MD simulations of three mitragynine compounds in lipid bilayer. Snapshots from the MD simulation trajectory show approximate time scales when the compounds entering the lipid bilayer region - (M1; red, M2; green, M3; blue).

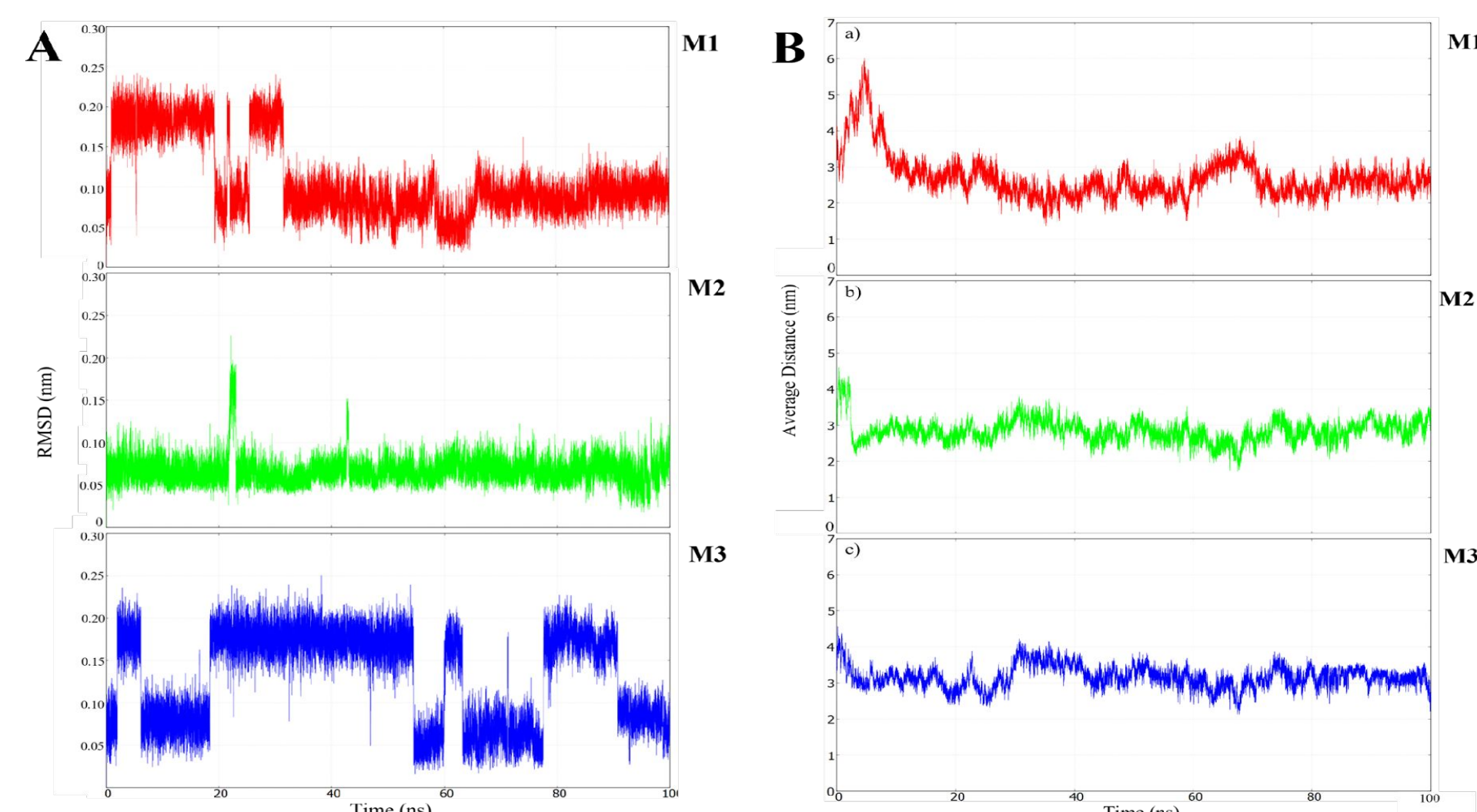


Figure 3A: Root Mean Square (RMSD) of 3 mitragynine during the MD simulation. M2 (green) has the most stable RMSD compared to M1 and M3.

Figure 3B: Average distance of mitragynine compounds to lipid headgroups. All the compounds started to move towards the lipid headgroups ~ 20 ns. M1 entered the bilayer ~23 ns, while M2 and M3 entered the bilayer ~57 ns. All three compounds remained in the position nearby the lipid headgroups below the lipid bilayer.

DISCUSSION

- Mitragynine compounds have physicochemical properties of hydrophilic as well as hydrophobic (4).
- Mitragynine able to enter the lipid bilayer faster as a single compound compared to a clumping or a group of compounds that could due to the high steric hindrance.
- After entering the lipid bilayer, all mitragynine compounds in the model system remained located nearby the lipid-water inter-phase to form hydrogen bonds with carbonyl and phosphate groups of lipids as well as water molecules.

CONCLUSION

In conclusion, mitragynine compounds able to enter lipid bilayer during 100 ns MD simulations. The compounds may enter as a single compound as well as in pair into the lipid bilayer region. The compounds positioned themselves below the lipid headgroups in order to form hydrogen bonds with the hydrophilic constituents of lipids and water molecules.

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