



In silico Binding Prediction of *Mitragyna speciosa* Alkaloids to Human Opioid Receptors

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INTRODUCTION

Kratom (*Mitragyna speciosa*), a tropical tree native to Southeast Asia, is traditionally used for its stimulant and sedative effects, which vary with dosage [1]. The primary alkaloids, mitragynine, and 7-hydroxymitragynine, are known for their significant pharmacological activities, especially in pain management, making kratom a subject of growing scientific interest and legal debate [2].

This study aims to bridge knowledge gaps by investigating the interactions of 35 distinct kratom alkaloids with the human mu (MOR), delta (DOR), and kappa (KOR) opioid receptors[3]. These receptors are crucial in modulating pain, mood, and addictive behaviors [4]. Using molecular docking, the binding affinities and receptor selectivity of these alkaloids were explored, shedding light on their pharmacological potential [5]. The aim is to identify the promising kratom alkaloids for the future development of better drugs for pain management and disease treatments.

METHODOLOGY

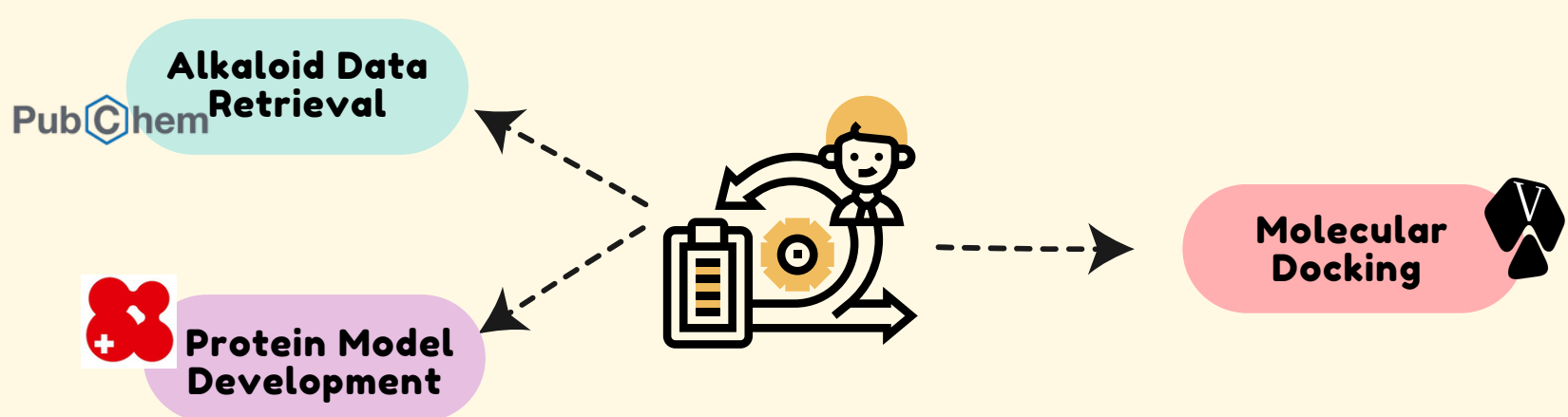


Figure 1 General workflow of methodologies.

OBJECTIVES

- (1) To evaluate binding affinities of 35 *Mitragyna speciosa* alkaloids to human delta (DOR), kappa (KOR), and mu (MOR) opioid receptors using molecular docking.
- (2) To identify binding site residues of the human opiod receptors that interacting with the kratom alkaloids

RESULTS & DISCUSSION

Table 1 Binding Affinities of Kratom Alkaloids to DOR, KOR and MOR

No	Alkaloid	PubChem ID	Binding affinity (kcal/mol)		
			DOR	KOR	MOR
1	Mitragynine	3034396	-7.76	-7.56	-8.52
2	7-hydroxymitragynine	44301524	-7.40	-8.17	-7.56
3	Speciogynine	15560577	-7.26	-8.05	-8.05
4	Corynoxine	10475115	-7.99	-7.88	-7.28
5	Corynantheidine	3000341	-7.66	-7.73	-9.11
6	Strictosidine	161336	-8.02	-8.78	-9.11
7	Paynantheine	3037629	-7.44	-7.97	-7.97
8	Speciociliatine	15560576	-8.22	-7.59	-8.35
9	Speciofoline	5379742	-6.96	-6.99	-8.07
10	Mitraciliatine	11741588	-8.17	-7.23	-7.72
11	Ajmalicine	441975	-8.41	-9.18	-9.44
12	Tetrahydroalstonine	72340	-8.15	-8.50	-8.94
13	Oxindole	321710	-6.47	-5.94	-6.54
14	Isorhynchophylline	3037048	-7.50	-7.89	-7.68
15	Isocorynoxine	3037448	-7.93	-9.04	-8.72
16	Indole	798	-6.29	-5.70	-6.02
17	Corynoxine	44568160	-7.56	-7.85	-8.35
18	Rhynchophylline	5281408	-7.82	-7.94	-8.48
19	Isomitraphylline	11726520	-9.24	-8.92	-8.76
20	Corynoxine B	10091424	-7.58	-7.20	-8.05
21	Mitraphylline	94160	-8.18	-8.17	-8.99
22	Mitragynine pseudoindoxyl	44301701	-7.31	-7.43	-7.69
23	9-Hydroxycorynantheidine	10927114	-7.80	-7.81	-8.56
24	Mitrafoline	5379743	-7.95	-7.35	-9.34
25	Akuammigine	1268096	-8.60	-8.81	-8.96
26	Akuammine	13491909	-7.86	-8.37	-7.45
27	Epicatechin	72276	-8.84	-8.95	-7.80
28	Pinoresinol	73399	-7.76	-8.14	-8.15
29	Methylcarboxylate	4284721	-7.76	-7.60	-8.13
30	Stipulatine	101289778	-7.62	-8.05	-7.54
31	N-Methyl-D-aspartate	22880	-4.63	-4.17	-4.39
32	O-desmethyltramadol	9838803	-6.62	-6.20	-7.23
33	Albuterol	2083	-6.22	-6.86	-7.06
34	Isopteropodine	9885603	-9.17	-8.10	-8.15
35	Speciophylline	168985	-8.14	-8.52	-8.26

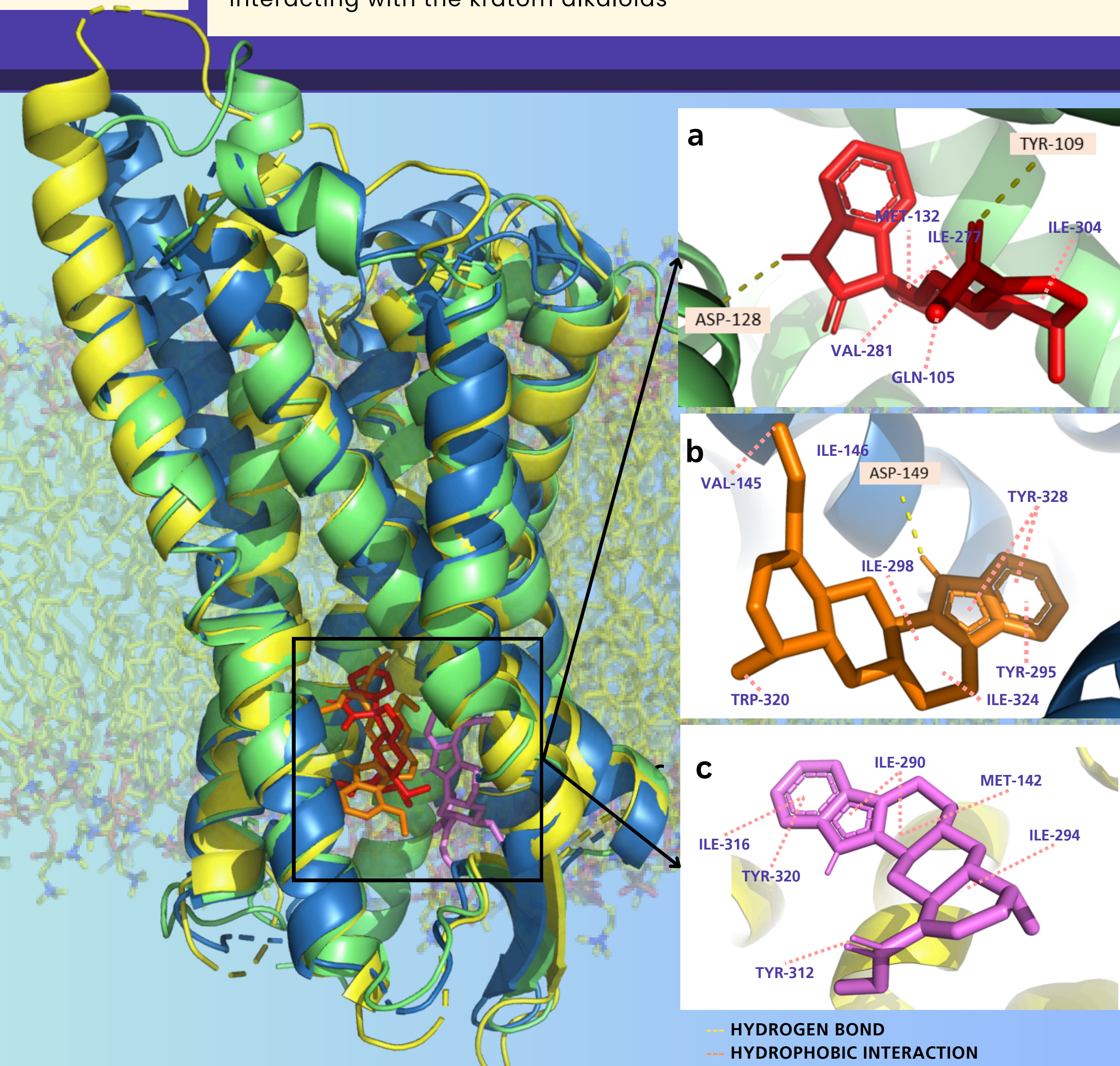


Figure 2 Docking of kratom alkaloids to the human opioid receptor, a) DOR (Green) b) MOR (Blue), and KOR (Yellow) bound to (a) Isomitraphylline, (b) Ajmalicine and (c) Ajmalicine

- The binding affinities of kratom alkaloids to the opiod receptors were range from -4.17 kcal/mol to -9.24 kcal/mol. Alkaloids with binding affinities greater than -9.0 kcal/mol include corynantheidine, strictosidine, ajmalicine, isomitraphylline, mitrafoline, and isopteropodine.
- Isomitraphylline demonstrates the highest binding affinity to the DOR with a binding energy of -9.24 kcal/mol, followed by isopteropodine (-9.17 kcal/mol) and epicatechin (-8.84 kcal/mol).
- Ajmalicine shows the highest binding affinity to the KOR at -9.18 kcal/mol, followed by isocorynoxine (-9.04 kcal/mol) and isomitraphylline (-8.92 kcal/mol).
- Ajmalicine also exhibits the highest binding affinity to the MOR with a binding energy of -9.44 kcal/mol, followed by corynoxine (-9.11 kcal/mol) and corynantheidine (-9.11 kcal/mol).
- Mitragynine has binding affinities of -7.76 kcal/mol for DOR, -7.56 kcal/mol for KOR, and -8.52 kcal/mol for MOR.
- In contrast, 7-hydroxymitragynine shows binding affinities of -7.40 kcal/mol for DOR, -8.17 kcal/mol for KOR, and -7.56 kcal/mol for MOR, indicating its strongest binding affinity is with the KOR.
- The lowest binding affinity is represented by N-methyl-D-aspartate, which shows a binding energy of -4.17 kcal/mol.

CONCLUSION

The molecular docking analysis of 35 alkaloids from *Mitragyna speciosa* with human opioid receptors identified several promising compounds that strongly bind to the human opioid receptors. The top alkaloids are isomitraphylline, soteropodine, epicatechin and ajmalicine. These alkaloids displayed favorable physicochemical properties and drug-like characteristics that potential for therapeutic agents. These results may contribute to the development of future drugs for pain management with less adverse effects.

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