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Original article

Molecular Docking and Binding Analysis of Phytochemicals from *Artemisia herba-Alba* and Coffee Targeting the Adenosine A_2A Receptor

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Abstract
Artemisia herba-alba is widely used in traditional medicine, particularly in North Africa, while coffee is one of the most consumed beverages worldwide. The use of medicinal plants together with dietary stimulants raises concerns about potential pharmacodynamic and pharmacokinetic interactions, especially at shared molecular targets. This study aimed to investigate the molecular interactions of caffeine, the major active constituents of coffee, and major bioactive constituents of *Artemisia herba-alba* (α-thujone and camphor) with the human adenosine A_2A receptor (A_2AR) using in silico molecular docking approaches. Blind molecular docking was performed using AutoDock Vina within PyRx and independently validated using the CB-Dock server. Binding affinities, cavity localization, and ligand–receptor interaction profiles were analyzed, and key hydrogen-bonding and hydrophobic interactions were characterized. All three ligands bound strongly to the orthosteric pocket of the adenosine A_2A receptor. α-thujone showed the strongest binding (–6.4 kcal/mol), followed by camphor (–6.1 kcal/mol) and caffeine (–5.8 to –6.1 kcal/mol). Cross-validation showed that the docking results were robust and reliable, with very small differences between platforms (< 0.3 kcal/mol). The ligands showed different binding patterns: α-thujone and camphor mainly interacted through hydrophobic contacts, while caffeine formed many hydrogen bonds. These findings suggest that compounds from *Artemisia herba-alba* can interact with the adenosine A_2A receptor at the same levels of caffeine, indicating a possible medicinal plant–food interaction. From a public-health and pharmacological point of view, using Artemisia preparations together with coffee may change the effects of caffeine and should therefore be studied further to ensure safe and informed use.
Keywords. *Artemisia herba-Alba*; Caffeine; Adenosine A_2A Receptor; Molecular Docking.

Introduction

Herbal medicine and traditional health practices continue to play a major role in global healthcare systems. According to the World Health Organization (WHO), nearly 80% of the world's population, particularly in developing countries, relies on medicinal plants as a primary or complementary form of healthcare. In parallel, the use of complementary and alternative medicine has increased in industrialized countries, driven by a growing preference for natural products and the long-term management of chronic diseases. This widespread use has intensified scientific interest in the safety, efficacy, and mechanisms of action of medicinal plants [1,2]. Libya has a rich botanical diversity because of its varied climatic and geographical regions. The use of medicinal plants is deeply embedded in Libyan culture, with numerous species traditionally employed for nutritional and therapeutic purposes [3]. One of the most important plant families is Asteraceae, which includes the genus Artemisia, known for its significant medicinal importance [4]. *Artemisia herba-alba*, commonly known as white wormwood (local name is Shih), is the most widely distributed Artemisia species in Libya and is traditionally used to treat metabolic, inflammatory, and infectious diseases [5]. Phytochemical studies of *A. herba-alba* showed a complex chemical composition of essential oils rich in oxygenated monoterpenes, particularly camphor and α-thujone, in addition to flavonoids, glycosides, tannins, and other secondary metabolites [6]. These compounds are associated with a wide range of pharmacological activities, including hypoglycemic, antioxidant, antimicrobial, anti-inflammatory, and anticancer effects [7].

Coffee, one of the most widely consumed beverages worldwide, is another significant source of bioactive compounds. Its major constituent, caffeine, is a well-known central nervous system stimulant that acts primarily as a non-selective antagonist of adenosine receptors, particularly the A_1 and A_2A subtypes. Coffee also contains chlorogenic acids which show antioxidant properties [8,9]. Both caffeine and *Artemisia* terpenoids are extensively metabolized by hepatic cytochrome P450 enzymes, raising concerns about possible metabolic interactions when consumed together [10,11]. In addition to metabolic interactions, caffeine exerts its pharmacological effects largely through antagonism of the adenosine A_2A receptor, a G protein-coupled receptor involved in neurological, cardiovascular, and immune functions [12]. In contrast, major *Artemisia* constituents such as camphor and α-thujone are not known to directly bind to the A_2A receptor; however, indirect modulation of adenosine signaling or competitive interactions at the metabolic level cannot be excluded [13]. Because herbal products and coffee are often used together, and there is increasing evidence that herbs can interact with drugs and beverages, it is important to predict these interactions. Molecular modeling is a useful computer-based method to study how these substances bind

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and interact with enzymes and receptors [14]. Therefore, this study aims to investigate the molecular interactions of selected phytochemicals from *Artemisia herba-alba* and coffee with targets related to metabolism and adenosine signaling, offering a theoretical framework to support safer use and guide future experimental studies.

Methods

The computational approach was used to investigate the potential interactions of caffeine and the major constituents of *Artemisia herba-alba* (α-thujone and camphor) with the human adenosine A_2A receptor (A_2AR). The methodology includes the selection of software tools and databases, retrieval and preparation of the receptor and ligands, blind molecular docking using two independent platforms (PyRx and CB-Dock), cross-validation of docking results, and detailed analysis of ligand–receptor interactions. This workflow was designed to allow unbiased exploration of possible binding sites and to ensure the reliability of the docking results.

Software, Databases, and Tools

Several freely available software packages and online databases were utilized: PyRx – Python Prescription (version 0.8) integrates AutoDock Vina and Open Babel and was used for ligand preparation (energy minimization and format conversion) and for blind molecular docking simulations [15]. AutoDock Tools (ADT) version 1.5.7 was employed for receptor preparation, including removal of heteroatoms, addition of polar hydrogens, assignment of Gasteiger charges, and conversion of the protein structure into PDBQT format required for AutoDock Vina [16]. Open Babel, integrated within PyRx, was used for chemical file format conversion, addition of hydrogen atoms, assignment of Gasteiger charges, and ligand energy minimization using the Universal Force Field (UFF) [17]. CB-Dock is an online blind docking server that detects binding cavities on the protein surface and performs docking using AutoDock Vina [18]. Ligands were submitted in SDF format to preserve consistency with the original PubChem structures. Ligand structures were retrieved from the NCBI PubChem database in SDF format, using their three-dimensional conformers. The compounds included caffeine (CID: 2519), α-thujone (CID: 261491), and camphor (CID: 2537) [19]. The crystal structure of the human adenosine A_2A receptor was obtained from the RCSB Protein Data Bank (PDB ID: 3EML). This structure represents the inactive receptor bound to the antagonist ZM241385 and provides a well-defined orthosteric binding pocket [20].

Protein Retrieval and Preparation

The three-dimensional structure of the human adenosine A_2A receptor (PDB ID: 3EML, resolution 2.6 Å) was downloaded in PDB format. The structure includes the co-crystallized ligand ZM241385, water molecules, and heteroatoms. Protein preparation was performed using AutoDock Tools (ADT) 1.5.7 as follows:

- Removal of heteroatoms: All water molecules, ions, and the co-crystallized ligand were removed.
- Addition of polar hydrogens: Polar hydrogen atoms were added to enable hydrogen bonding interactions.
- Assignment of charges: Gasteiger charges were assigned to all receptor atoms.
- Format conversion: The prepared receptor was saved in PDBQT format for docking.

Ligand Retrieval and Preparation

Ligand structures of caffeine, α-thujone, and camphor were obtained from PubChem as three-dimensional SDF files. Their physicochemical properties are as follows: Caffeine (CID 2519): $C_8H_{10}N_4O_2$, MW 194.19 g/mol, α-Thujone (CID 261491): $C_{10}H_{16}O$, MW 152.23 g/mol, Camphor (CID 2537): $C_{10}H_{16}O$, MW 152.23 g/mol. Camphor and α-thujone were selected due to their high abundance in *Artemisia herba-alba* and represent the major chemotypes [19].

Ligand preparation in PyRx included

- Import of SDF files
- Energy minimization using UFF until no further change (<0.1 kcal/mol·Å)
- Addition of hydrogen atoms and Gasteiger charges
- Assignment of rotatable bonds
- Conversion to PDBQT format

Blind Docking Using PyRx

Docking simulations were conducted using AutoDock Vina within PyRx. A blind docking approach was applied to allow free study of the entire receptor surface.

Grid Box Parameters

A grid box of 80 × 80 × 80 Å was centered to include the entire receptor. The position of the known orthosteric site was recorded only for reference and was not used to limit the docking process.

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Docking Settings
The exhaustiveness parameter was set to 16 to balance accuracy and computational efficiency. Each ligand was docked separately, generating up to nine poses. The pose with the lowest binding energy (ΔG, kcal/mol) was selected for further analysis. Docking runs were performed in triplicate [20].

Cross-Validation Using CB-Dock
Independent validation was performed using CB-Dock, which combines cavity detection with AutoDock Vina-based docking. The prepared receptor and ligands were submitted without user-defined binding sites. Docking results from CB-Dock were compared with those obtained from PyRx. Results were considered consistent if binding affinity differences were ≤1.0 kcal/mol.

Interaction Analysis
The best-ranked docking poses from CB-Dock were analyzed using UCSF Chimera version 1.17.3. Hydrogen bonds were identified using the FindHBond tool (distance cutoff ≤ 4.0 Å; angle ≥ 120°), while hydrophobic and van der Waals contacts were detected using the Contacts tool with a cutoff of 5.0 Å. Interacting residues were visualized in stick representation, and figures were prepared using a white background.
For each complex, hydrogen bonds and close contacts were recorded along with interacting residues, atom names, distances, and overlap values.

Results
Blind docking simulations were conducted using the AutoDock Vina engine within the PyRx environment to evaluate the binding of caffeine (CID: 2519), camphor (CID: 2537), and α-thujone (CID: 261491) to the human adenosine A_2A receptor (PDB ID: 3EML). For each ligand, nine binding poses were generated. The optimal binding pose was selected based on the lowest predicted binding free energy (ΔG). A summary of the docking scores and selected binding poses is presented in (Table 1).

Table 1. Best Binding Affinities from PyRx Blind Docking

Best \ G (kcal/mol)	Ligand
-5.8	Caffeine (CID:2519)
-6.1	Camphor (CID:2537)
-6.3	α-thujone

All three ligands exhibited significant binding affinities toward the adenosine A_2A receptor. Among them, α-thujone showed the strongest binding affinity (–6.3 kcal/mol), followed by camphor (–6.1 kcal/mol) and caffeine (–5.8 kcal/mol).

Interaction Analysis of Top-Ranked Poses from CB-Dock
To obtain detailed information on ligand receptor binding modes, the top-ranked docking poses generated by the CB-Dock server used for independent cross-validation were visualized and analyzed using UCSF Chimera. The predicted binding affinities for the best poses were –6.1 kcal/mol for caffeine (cavity 2), –6.4 kcal/mol for α-thujone (cavity 3), and –6.1 kcal/mol for camphor (cavity 3).

Caffeine (CID: 2519)
The top-ranked docking pose of caffeine obtained from CB-Dock (ΔG = –6.1 kcal/mol) was further analyzed using UCSF Chimera to characterize its interaction profile with the adenosine A_2A receptor. The analysis revealed a total of 17 hydrogen bonds and 35 close contacts between caffeine and receptor residues. The main hydrogen-bond interactions are summarized in (Table 2), while the most significant close contacts are presented in (Table 3).

Table 2. Key Hydrogen Bonds in Caffeine-A_2AR Complex (Chimera Analysis)

Distance D-A(Å)	Acceptor	Donor
2.459	4NL1.AO	ARG1008.A NH2
2.260	4NL1.AO	LE41013.AN
3.241	4NL1.AO	ARG1008.A NE
3.382	4NL1.AO	ARG206.A NH2

Table 3. Key Close Contacts in Caffeine-A_2AR Complex (Chimera Analysis)

Distances (Å)	Overlap (Å)	Receptor/Residue Atom	Ligand Atom
2.536	0.344	ARG1008.A HE	UNL1.A C
2.260	0.160	LE4103.A HN	UNL1.A O
3.598	0.042	ILE1009.A CA	UNL1.A C

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3.008	0.037	ARG1008.A NH2	UNL1.A O
3.754	0.006	LE41013.A CB	UNL1.A C

The shortest hydrogen bond was observed between the NH_2 group of ARG1008. A and the carbonyl oxygen of caffeine, with a bond distance of 2.459 Å. Additional hydrogen bonds involved LEU1013. A and ARG206.A, indicating the presence of a complex network of polar interactions that holds caffeine within the orthosteric binding pocket of the receptor (Figure 1). Furthermore, interactions with ILE1009.A, PRO109.A, and GLY1012.A contributed to complex stabilization through hydrophobic and van der Waals contacts.

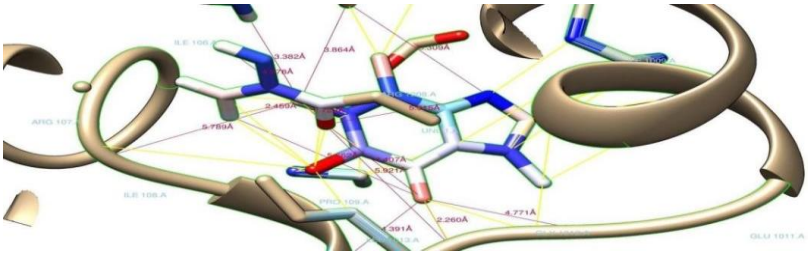

Figure 1. Chimera image showing caffeine (UNL 1.A) with ARG1008, LEU1013, and ARG206, annotated with hydrogen bond distances

α-Thujone (CID: 261491)

The top-ranked docking pose of α-thujone obtained from the CB-Dock server (ΔG = –6.4 kcal/mol) was analyzed using UCSF Chimera to characterize its interaction profile with the adenosine A_2A receptor. The analysis identified a total of 7 hydrogen bonds and 30 close contacts between α-thujone and receptor residues. The key hydrogen-bond interactions are summarized in (Table 4), whereas the most significant close contacts are presented in (Table 5).

Table 4. Key Hydrogen Bonds in α-Thujone-A_2AR Complex (Chimera Analysis)

Distances D-A(Å)	Acceptor	Donor
2.069	4NL1.A C	HIS278.A HE2

Table 5. Key Close Contacts in α-Thujone-A_2AR Complex (Chimera Analysis)

Distance (Å)	Overlap (Å)	Receptor Residue/ Atom	Ligand
2.069	0.351	HIS278.A HE2	UNL 1.A C
3.433	0.327	VAL84.A CG1	UNL 1.A C
3.580	0.180	ILE274.A CD1	UNL 1.A C
3.556	0.084	PHE168.A CE1	UNL 1.A C
3.691	0.069	ALA63.A CB	UNL 1.A C
3.031	0.014	HIS278.A NE2	UNL 1.A C

The strongest interaction was a hydrogen bond formed between the HE2 atom of HIS278. A and α-thujone, with a bond distance of 2.069 Å. In addition, extensive hydrophobic interactions with VAL84.A, ILE274.A, PHE168.A, and ALA63.A contributed to stabilization of the ligand–receptor complex and are consistent with the observed high binding affinity (–6.4 kcal/mol). The ligand was deeply embedded within a hydrophobic cleft of the receptor, a binding mode that aligns well with the nonpolar, bicyclic structure of α-thujone (Figure 2).

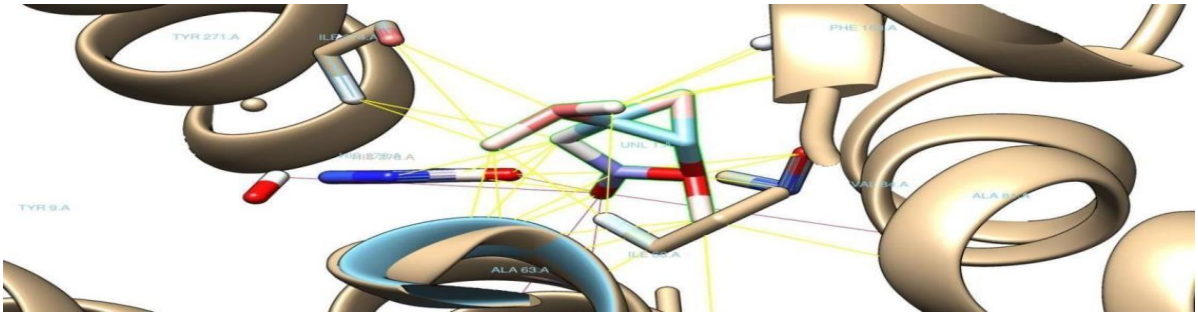

Figure 2. Chimera image showing α-thujone with HIS278, VAL84, ILE274, PHE168, and ALA63, annotated with hydrogen bond and contact distances

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Camphor (CID: 2537)

The top-ranked docking pose of camphor obtained from the CB-Dock server (ΔG = –6.1 kcal/mol) was analyzed using UCSF Chimera to characterize its interaction pattern with the adenosine A_2A receptor. The analysis identified a total of 7 hydrogen bonds and 27 close contacts between camphor and receptor residues. The key hydrogen-bond interactions are summarized in (Table 6), while the most significant close contacts are presented in (Table 7).

Table 6. Key Hydrogen Bonds/ polar electrostatic contact in Camphor-A_2AR Complex (Chimera Analysis)

Distance D-A(Å)	Acceptor	Donor
3.910	UNL 1.A O1	ALA 63 A N
5.194	UNL 1.A O1	VAL 84 A N
5.243	UNL 1.A O1	HIS 278 A NH2
5.866	UNL 1.A O1	PHE 62 A N
6.187	UNL 1.A O1	PHE 83 A N
6.272	UNL 1.A O1	ILE 64 A N
6.672	UNL 1.A O	LE4 85 A N

Table 7. Key Close Contacts in Camphor-A_2AR Complex (Chimera Analysis)

Distance (Å)	Overlap (Å)	Receptor Residue/ Atom	Ligand Atom
2.622	0.258	HIS 278 A HE2	UNL 1.A C6
3.336	0.424	ILE 274 A CG2	UNL 1.A C5
3.407	0.233	PHE 168. A CD1	UNL 1.A C10
3.555	0.205	ILE66 A CG2	UNL 1.A C4
3.573	0.187	VAL 84 A CG1	UNL 1.A C8
3.643	0.117	ILE 274 A CD1	UNL 1.A C5
3.651	0.109	ALA 63 A CA	UNL 1.A C4
3.678	0.082	ALA 81 A CA	UNL 1.A C10
3.559	0.081	PHE 168 A CE1	UNL 1.A C8
3.682	0.078	ALA 63 A CB	UNL 1.A C5

Camphor displayed a binding mode distinct from that of caffeine, interacting primarily with PHE62.A, ALA63.A, ILE64.A, PHE83.A, VAL84.A, LEU85.A, and HIS278. A through hydrogen-bond interactions, and with ILE274.A, HIS278.A, PHE168.A, ILE66.A, VAL84.A, ALA63.A, and ALA81.A via close hydrophobic and van der Waals contacts. Despite occupying a different binding region within the receptor, camphor exhibited a binding affinity of –6.1 kcal/mol, comparable to that of caffeine (Figure 3). This finding indicates that camphor can bind to the adenosine A_2A receptor with similar binding strength through an alternative binding mode.

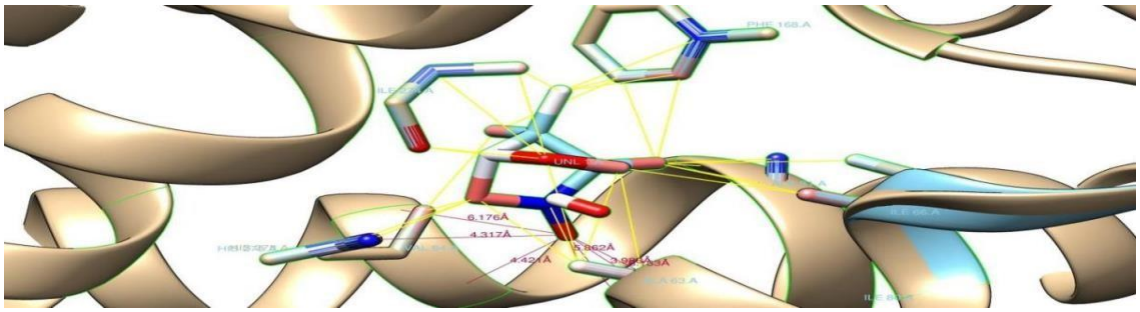

Figure 3. Chimera image showing (camphor with ALA63, VAL84, HIS278, ILE274, and PHE168, annotated with hydrogen bond and contact distances

Cross-Validation Using CB-Dock

Independent blind docking simulations were performed using the CB-Dock web server to validate the docking results obtained from PyRx. The comparison focused on binding affinities and the ranking of identified binding cavities for each ligand. The best predicted binding affinities and corresponding cavity ranks from both docking platforms are summarized in (Table 8).

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Table 8. Comparison of binding affinities (ΔG, kcal/mol) and cavity rankings obtained from PyRx and CB-Dock for caffeine, α-thujone, and camphor

Difference	CB-Dock Best G (Kcal/mol)	PyRx Best G (Kcal /mol)	Ligand
0.3	-6.1	-5.8	Caffeine
0.0	-6.1	-6.1	Camphor
0.1	-6.4	-6.3	α-Thujon

All differences in binding affinities between PyRx and CB-Dock were within the acceptable limit (< 1.0 kcal/mol), confirming the strength and reliability of the docking protocol. For camphor and α-thujone, the predicted binding affinities were virtually identical across both platforms, while caffeine exhibited a minor yet acceptable variation of 0.3 kcal/mol. In all cases, the highest-ranked cavities identified by CB-Dock corresponded to the orthosteric binding pocket, in agreement with the PyRx docking predictions.

Discussion

Blind docking of caffeine, α-thujone, and camphor against the human adenosine A_2A receptor (A_2AR) produced constant binding affinity estimates using two independent workflows: AutoDock Vina implemented in PyRx and the CB-Dock blind-docking server. The receptor structure used (PDB ID: 3EML) is an inactive-state A_2AR crystal structure co-crystallized with the antagonist ZM241385, providing a well-defined orthosteric pocket suitable for docking studies [17,19,12]. Among the tested ligands, α-thujone showed the strongest predicted binding (ΔG ≈ −6.4 kcal/mol), whereas camphor and caffeine were similar (ΔG ≈ −6.1 kcal/mol; caffeine also −5.8 kcal/mol in PyRx). Since caffeine is a known adenosine receptor blocker, the slightly stronger binding of α-thujone suggests it may bind to the same site, but this needs experimental confirmation [21,12]. The interaction patterns were different for each type of compound.

Caffeine was formed several polar interactions inside the binding pocket, which agrees with its known ability to bind adenosine receptors. In contrast, α-thujone and camphor, the main components of *Artemisia herba-alba* essential oil, were mainly stabilized by hydrophobic interactions, with fewer and weaker polar interactions. Overall, the docking results suggest the following order of binding strength: α-thujone > camphor ≈ caffeine [21,22]. Since caffeine is mainly metabolized by CYP1A2 and α-thujone is also metabolized by CYP enzymes, there may be pharmacokinetic interactions in addition to competition at the receptor level, but this needs to be confirmed by experimental studies [23]. This finding is significant because α-thujone can affect the nervous system by acting on $GABA_A$ receptors at higher doses; therefore, its safety profile and dosing require careful assessment during co-administration [24].

Conclusion

This study underscores the public-health relevance of medicinal plant–food interactions by demonstrating that major constituents of *Artemisia herba-alba*, particularly α-thujone and camphor, can interact with the adenosine A_2A receptor with binding affinities comparable to caffeine. Given the traditional use of *Artemisia herba-alba* and the consumption of coffee, the same time intake may alter expected pharmacological effects through both receptor-level (pharmacodynamic) and metabolic (pharmacokinetic) mechanisms. These findings highlight the importance of considering everyday dietary factors when evaluating the safety and efficacy of medicinal plants. These findings highlight the need for further experimental validation and support the importance of evidence-based guidance to ensure safe and informed use of herbal medicines with daily consumed beverages.

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Conflicts of Interest

This research received no external funding.

References

1. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Neurol. 2014;4:1–10.
2. Bodeker G, Kronenberg F. A public health agenda for traditional, complementary, and alternative medicine. Am J Public Health. 2002;92(10):1582–91.
3. Mahklouf MH. Ethnobotanical study of edible wild plants in Libya. Eur J Ecol. 2019;5(2):30–40.
4. Al-Sghair FG, Mohammed MA. Floristic analysis of the family Asteraceae in Libya depending on flora of Libya. Am J Life Sci Res. 2017;5(4):170–83.
5. Bora KS, Sharma A. The genus Artemisia: a comprehensive review. Pharm Biol. 2011;49(1):101–9.
6. Giweli A, Ben A. Camphor–thujone chemotype and bioactivities of *Artemisia herba-alba* Asso essential oil from Zintan, Libya: chemical composition, antibacterial, and antiproliferative effects. Alqalam J Med Appl Sci. 2025;8(4):2578–85.

Received*: 28-10-2025 -* ***Accepted****: 21-12-2025 -* ***Published****: 30-12-2025*

7. Mahboub N, Laib I, Bennaceur D, Meraghni A, Kherroubi H. Phytochemical profiling of *Artemisia herba-alba* Asso by HPLC analysis and investigation of the antioxidant and antibacterial activities. Analele Univ Oradea Fasc Biol. 2024;(Vitamin C):167–74.
8. Carvalho Neto DP de, Gonot-Schoupinsky XP, Gonot-Schoupinsky FN. Coffee as a naturally beneficial and sustainable ingredient in personal care products: a systematic scoping review of the evidence. Front Sustain. 2021;2(October).
9. van Dam RM, Hu FB, Willett WC. Coffee, caffeine, and health. N Engl J Med. 2020;383(4):369–78.
10. Grzegorzewski J, Bartsch F, Köller A, König M. Pharmacokinetics of caffeine: a systematic analysis of reported data for application in metabolic phenotyping and liver function testing. Front Pharmacol. 2022;12(February).
11. Sen A. Complementary medicines used in ulcerative colitis and unintended interactions with cytochrome P450-dependent drug-metabolizing enzymes. Turk J Med Sci. 2022;52(5):1425–47.
12. Jacobson KA, Gao Z, Eddy MT, Carlsson J. Adenosine A2A receptor antagonists: from caffeine to selective non-xanthines. Br J Pharmacol. 2022;179(14):3496–511.
13. Lee J, Narayan VP, Hong EY, Whang WK, Park T. Artemisia iwayomogi extract attenuates high-fat diet-induced hypertriglyceridemia in mice: potential involvement of the adiponectin-AMPK pathway and very low density lipoprotein assembly in the liver. Int J Mol Sci. 2017;18(8).
14. Hemaiswarya S, Prabhakar PK, Doble M. Computational Methods to Study Herb–Drug Interactions. Springer; 2022:235–44.
15. Abriata LA. Structural database resources for biological macromolecules. Brief Bioinform. 2017;18(4):659–69.
16. Forli S, Huey R, Pique ME, Sanner MF, Goodsell DS, Olson AJ. Computational protein–ligand docking and virtual drug screening with the AutoDock suite. Nat Protoc. 2016;11:905–19.
17. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. In: Methods in Molecular Biology. Vol 1263. Springer; 2015:243–50.
18. Liu Y, Grimm M, Dai WT, Hou MC, Xiao ZX, Cao Y. CB-Dock: a web server for cavity detection-guided protein–ligand blind docking. Acta Pharmacol Sin. 2020;41:138–44.
19. Bolton EE, Kim S, Bryant SH. PubChem3D: conformer generation. J Cheminform. 2011;3(4):1–16.
20. Jaakola VP, Griffith MT, Hanson MA, Cherezov V, Chien EYT, Lane JR, et al. The 2.6 Å crystal structure of a human A2A adenosine receptor bound to an antagonist. Science. 2008;322(5905):1211–7.
21. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, Ferrin TE. UCSF Chimera—a visualization system for exploratory research and analysis. J Comput Chem. 2004;25(13):1605–12.
22. Robertson N, Errey JC, Ng I, Hollenstein K, Tehan B, Hurrell E, et al. Structure of the adenosine A2A receptor in complex with ZM241385 and the xanthines XAC and caffeine. Cell Press. 2011;4:1283–93.
23. Pelkonen O, Abass K, Wiesner J. Thujone and thujone-containing herbal medicinal and botanical products: toxicological assessment. Regul Toxicol Pharmacol. 2013;65(1):100–7.
24. Höld KM, Sirisoma NS, Ikeda T, Narahashi T, Casida JE. α-Thujone: GABAA receptor modulation and metabolic detoxification. Proc Natl Acad Sci USA. 2000;97(8):3826–31.

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