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"Sleepless in Cannes Not Anymore - The Science of Sleep-Inducing Scents"

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1. Introduction

Sleep is a fundamental biological process essential for immune function, tissue repair, memory consolidation, and emotional regulation. Despite its critical role in both physical and mental health, approximately one-third of the global population suffers from sleep insufficiency [1,2]. This widespread disturbance—often attributed to excessive screen exposure, psychological stress, and irregular daily rhythms—has emerged as a hallmark of modern life. Chronic sleep deprivation is strongly associated with increased risks of type 2 diabetes, cardiovascular disease, and neuropsychiatric conditions, including anxiety and depression [3]. As the global burden of insomnia and sleep-related disorders rises, so too does the demand for non-pharmacological interventions. Conventional pharmacotherapies, though effective, present concerns such as tolerance, dependence, and side effects, leading to growing public and scientific interest in alternative modalities. Among these, aromatherapy—the controlled use of essential oils and fragrance compounds—has gained attention as a promising approach to enhance sleep and reduce anxiety by modulating the autonomic and limbic systems through the olfactory pathway [4]. Historically regarded as a mystical or holistic practice, aromatherapy is now undergoing a paradigm shift into the scientific realm. Recent studies have begun to explore its mechanisms using neuroimaging, biochemical assays, and molecular modeling, aiming to transition the field from anecdotal tradition to empirical science. This shift is reflected in the rapid growth of academic interest: according to a PubMed bibliometric survey, the number of aromatherapy-related publications has increased at a compound annual growth rate (CAGR) of 9.7% over the past decade, indicating a significant uptick in scientific engagement. The efficacy of aromatherapy has been consistently demonstrated through clinical trials. For example, the nhalation of essential oils such as lavender, bergamot, and ylang-ylang has been shown—through polysomnographic analyses and self-report surveys—to reduce sleep latency, prolong total sleep time, and alleviate anxiety symptoms [5,6]. These findings suggest that aroma compounds may exert influence on neurotransmitter systems, particularly inhibitory GABAergic pathways, leading to a natural extension of research into their molecular and neurobiological mechanisms.

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system, maintaining neural stability by attenuating excitatory signals [7]. The $GABA_A$ receptor, a ligand-gated chloride channel composed of α, β, and γ subunits, plays a key role

in mediating sedation and emotional regulation. It is abundantly expressed in the limbic system, especially the amygdala, a structure crucial for processing fear and anxiety [8]. The structural arrangement of this receptor and its ligand-binding topology are depicted in Figure 1, highlighting the distinct subunit composition and the native binding interfaces for GABA and diazepam. Uniquely, the olfactory system projects directly to the limbic cortex, bypassing the thalamus, thus allowing odor signals to directly influence emotional and autonomic responses [9]. This anatomical configuration supports the plausibility of fragrance compounds modulating neurochemical pathways relevant to sleep and emotional states.

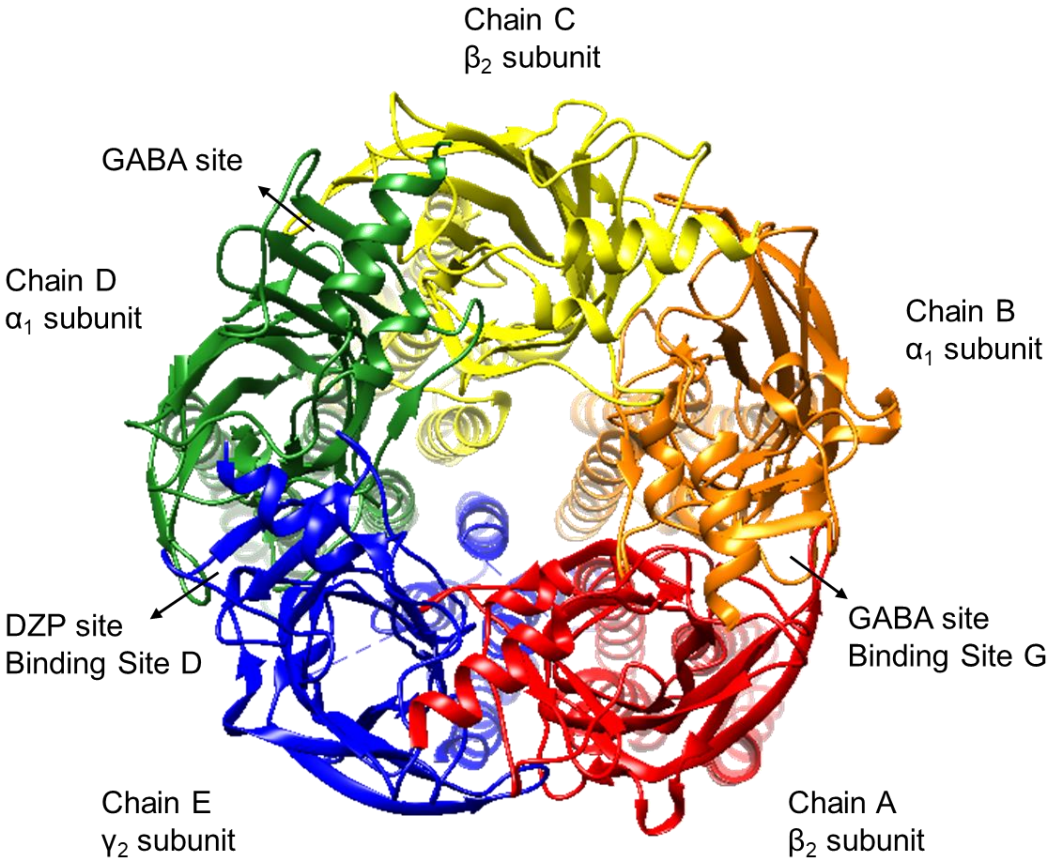

Figure 1. Structural topology of the $GABA_A$ receptor highlighting ligand binding sites. Color-coded subunits (Chain A–E) of the human $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptor(PDB: 6D6U) are shown in cartoon representation. Each chain is represented as follows: Chain A (β_2, red), Chain B (α_1, orange), Chain C (β_2, yellow), Chain D (α_1, green), and Chain E (γ_2, blue). The native GABA binding site is located at the interface between the α_1 and β_2 subunits, while the DZP binding site lies between the α_1 and γ_2 subunits.

While most prior studies have adopted a top-down strategy—inferring mechanisms using *in silico* methods from observed physiological outcomes—this research employs a bottom-up approach, beginning with the molecular interactions between fragrance compounds and the $GABA_A$ receptor. Utilizing structure-based *in silico* docking and a customized cutoff-based screening pipeline, we systematically identified candidate ligands. This approach enhances screening efficiency while offering mechanistic insights at the molecular level. Through this study, we aim to contribute meaningfully to the advancement of evidence-based holistic science.

2. Materials and Methods

2.1. Receptor Selection and Structure Preparation

In this study, two distinct binding sites within the $GABA_A$ receptor were identified as targets for exploration: the GABA binding site, referred to as Binding Site G, and the benzodiazepines binding site, referred to as Binding Site D. We selected PDB entry 6D6U for the receptor model to utilize the electron microscopy protein structure file of the $GABA_A$ receptor docked with the GABA compound in its experimental structure. This choice was based on Zhu et al.'s structural insights, which provided an accurate model for Binding Site G [10]. Conversely, PDB entry 6X3X was chosen because it supplies the electron microscopy protein structure file of the $GABA_A$ receptor docked with diazepam(DZP), giving us an accurate model for Binding Site D [11]. To ensure a seamless comparison of coordinates, vector adjustments were performed on subunits D and E of PDB file 6X3X to align them with 6D6U's coordinates. This alignment enables accurate mapping of DZP's binding to the 6D6U structure.

2.2. Ligand Collection and Structure Preparation

Ligand data were sourced from the International Fragrance Association (IFRA) 2020 Fragrance Ingredient Glossary, which lists 2,225 fragrance components [12]. We narrowed our selection to 1,925 ligands, eliminating natural fragrances and some chemicals that are unavailable for preparing SMILES structures and ensuring data reliability. Ligand structures were prepared by converting SMILES strings to 3D molecular coordinates, leveraging cheminformatics libraries [13], and subsequently converting these to PDB and PDBQT formats. The PDBQT conversion, performed using Open Babel, computed partial charges using the Gasteiger charge model [14,15]. Throughout these steps, the ligand names and original SMILES expressions were documented as remarks within the PDBQT files to maintain traceability and reference for subsequent docking analyses. This process ensured that all ligands were uniformly prepared and optimized for docking simulations with the $GABA_A$ receptor targets.

2.3. Docking simulation

For the docking simulations, AutoDock Vina (version 1.2.3-2) was used [16,17]. Each ligand was independently docked onto both designated binding sites, G and D, and the results were preserved for comprehensive analysis. The search space was defined with dimensions of 20 Å × 20 Å × 20 Å for each axis (size_x, size_y, size_z), concentrating the exploration around the binding sites. The exhaustiveness was set to 4, and the num_modes parameter was set to 9, ensuring efficient exploration of possible binding modes. Center coordinates were specifically defined to accurately position the docking grid, with binding site G centered at x = 151.56, y = 164.11, z = 113.48 based on the GABA binding position observed in PDB entry 6D6U. For binding site D, the center coordinates were x = 117.95, y = 166.00, z = 153.42, based on the DZP binding position originally modeled in PDB entry 6X3X, aligned to the 6D6U coordinate framework.

2.4. Cutoff Criteria Establishment

To systematically identify fragrance ligands with high potential for interaction with the $GABA_A$ receptor, we established a set of cutoff criteria uniquely tailored for Binding Sites G and D. Initially, GABA and DZP were docked to their respective native binding sites, generating nine poses each through conformational sampling. From these, the poses with centroids most closely aligned to the experimentally bound ligand coordinates were selected as reference models. The cutoff criteria were based on three docking-derived parameters: (1) the Euclidean distance between the centroid of the docking model and the corresponding binding site, (2) the

predicted binding affinity, and (3) the proportion of overlapping residues within 4 Å compared to the reference residue set. For Binding Site G, amino acid residues located within 4 Å of the reference model's centroid included Y157.A, F200.A, T202.A, Y205.A, F65.B, R67.B, and T130.B (seven in total). For Binding Site D, twelve residues were similarly identified: F100.D, H102.D, Y160.D, A161.D, V203.D, S205.D, S206.D, T207.D, Y210.D, V212.D, Y58.E, and F77.E. These residues were not selected based on prior functional annotation, but were objectively derived from spatial proximity to the docked ligands in this study. Many of the identified residues are enriched in aromatic side chains, collectively forming binding pockets that are conducive to π-π stacking and other non-covalent interactions implicated in receptor modulation. To streamline the screening of over a thousand ligands, we employed a pragmatic cutoff framework: candidate models were retained only if their distance and binding affinity were equal to or better than (i.e., lower than) the reference values, and their residue similarity was equal to or greater than the reference threshold. This approach balances biological relevance and computational efficiency, ensuring rapid yet reliable identification of fragrance compounds with promising receptor engagement profiles.

2.5. Evaluation of Aromatic Compounds' Effect on Sleep Quality

To gain preliminary insights into the potential sleep-related effects of fragrance compounds, we conducted a small-scale exploratory evaluation as an extension of our docking-based screening protocol. Two ingredients—vanillin (CAS 121-33-5) and anethole (CAS 104-46-1)—were identified through our cutoff-based selection framework and further considered for testing. A basic 12-day protocol was designed to assess sleep changes associated with fragrance exposure, incorporating control and treatment periods. While not a formal clinical trial, the protocol included a baseline control day followed by three consecutive days of testing with each compound, interspersed with additional fragrance-free control days. For this pilot test, 9 healthy individuals in their 30s, voluntarily participated. Scent strips (13.5 cm × 0.5 cm) were used, with participants immersing the tip in the prepared solution and inhaling for one minute prior to sleep. The strips were then placed within 20 cm of the nose throughout the night, alongside an iPhone 11 Pro (Apple Inc.) equipped with a sleep-monitoring mobile application (SleepRoutine, Asleep; South Korea). Sleep quality was assessed using two basic metrics: sleep latency (the time taken to fall asleep) and sleep efficiency (the percentage of time spent sleeping versus total time in bed). While results are not conclusive due to the study's limited scale and informal setting, this preliminary effort provided practical validation for the proposed fragrance screening approach and highlighted key methodological considerations for future controlled sleep studies.

3. Results

3.1. Native Ligand-Based Definition of Docking Cutoffs

To ensure the validity of our docking simulations, we initially docked the native ligands—GABA and DZP—to their respective binding sites within the $GABA_A$ receptor: Binding Site G and Binding Site D. Each ligand produced nine docking poses, and the pose exhibiting the closest spatial proximity to the crystallographically observed binding position was selected as the reference model. For GABA, the selected pose demonstrated a centroid distance of 0.59 Å from the Binding Site G center and a binding affinity of –3.81 kcal/mol, with 100% similarity in surrounding residues within 4 Å compared to the experimental GABA pose in PDB 6D6U. Similarly, for DZP, the best pose exhibited a centroid distance of 1.74 Å, a binding affinity of –8.08 kcal/mol, and a 83.33% overlap in surrounding residues, aligned to the diazepam binding

configuration of PDB 6X3X realigned to 6D6U. These results served as the basis for defining cutoff thresholds in subsequent large-scale ligand screening.

3.2. Application of Cutoff Criteria and Screening Outcomes

To assess the engagement potential of fragrance ligands with the $GABA_A$ receptor, the previously established cutoff criteria were applied across the entire ligand dataset. From a total of 1,925 screened compounds, 116 ligands targeting Binding Site G and 16 ligands targeting Binding Site D satisfied all three criteria simultaneously: spatial proximity within the binding pocket, favorable binding affinity, and high residue-level similarity with the native ligand.

3.3. Visual Comparison of Binding Poses

3.3.1. Binding Site G

To qualitatively assess the reliability of the docking protocol and the spatial accuracy of ligand poses, we compared the three-dimensional alignments of the experimentally resolved GABA conformation with docking-derived models. As shown in Figure 2a, the crystallographic binding pose of GABA within the $GABA_A$ receptor 's Binding Site G served as the structural reference. Figure 2b illustrates the top-ranked docked pose of GABA, which exhibited high concordance with the native configuration, thus validating the accuracy of the docking workflow. Among the 1,925 screened fragrance compounds, 4-hydroxybenzaldehyde emerged as the most structurally congruent candidate. As presented in Figure 2c, its binding pose demonstrated an exceptional spatial overlap with the reference ligand, achieving a centroid distance of 0.07 Å, a binding affinity of –6.18 kcal/mol, and 100% residue similarity within a 4 Å interaction radius. These metrics collectively indicate a highly favorable fit within the GABA binding pocket. In contrast, butyl phenylacetate, depicted in Figure 2d, exemplified a low-fit docking profile. Its pose was characterized by the greatest spatial deviation, with a centroid distance of 12.04 Å, a notably weaker binding affinity of –4.22 kcal/mol, and a residue similarity of only 29% compared to the GABA reference.

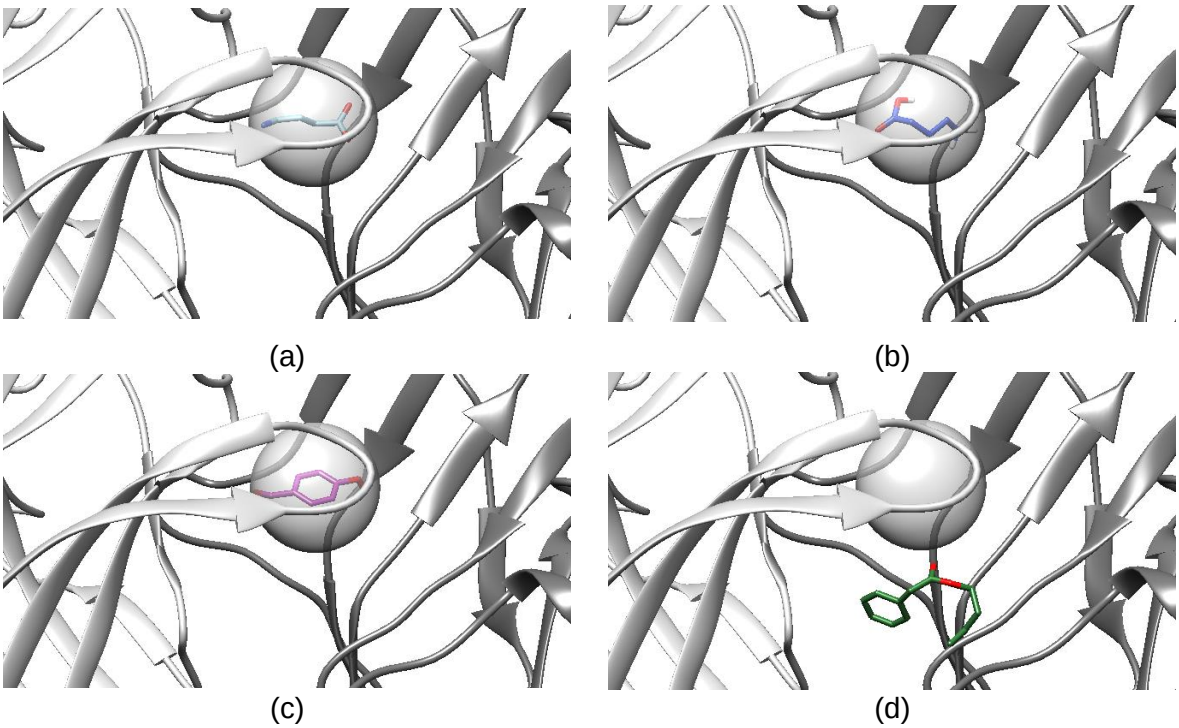

Figure 2. Comparative binding poses of GABA and ligands within the $GABA_A$ receptor (PDB: 6D6U). The receptor is visualized with chain A (β_2 subunit) in light gray and chain B (α_1 subunit) in dim gray ribbon representation. A semi-transparent gray sphere (4 Å radius) denotes the center of Binding Site G, serving as a spatial reference for ligand localization. (a) GABA (crystal structure); (b) GABA (docked pose); (c) 4-Hydroxybenzaldehyde; (d) Butyl phenylacetate.

3.3.2. Binding Site D

We conducted a parallel visual analysis for ligands targeting Binding Site D. Figure 3a shows the binding pose of diazepam (DZP) from the experimentally resolved structure (PDB 6X3X), realigned to the 6D6U coordinate space. The corresponding docked pose obtained from our simulation (Figure 3b) closely recapitulated this reference configuration, confirming the robustness of our docking approach for the benzodiazepine binding site. Among the screened ligands, β-caryophyllene acetate (Figure 3c) was identified as the most spatially aligned candidate within the cutoff criteria. It achieved a centroid distance of 0.70 Å, a binding affinity of –8.83 kcal/mol, and a residue similarity of 83%, indicating a high degree of compatibility with the DZP binding pocket. In contrast, farnesol (Figure 3d) was found at the opposite end of the spectrum. Despite meeting the residue similarity threshold (83%), its binding pose deviated substantially, with a centroid distance of 4.68 Å and a reduced affinity of –6.96 kcal/mol, reflecting a less optimal fit within the site.

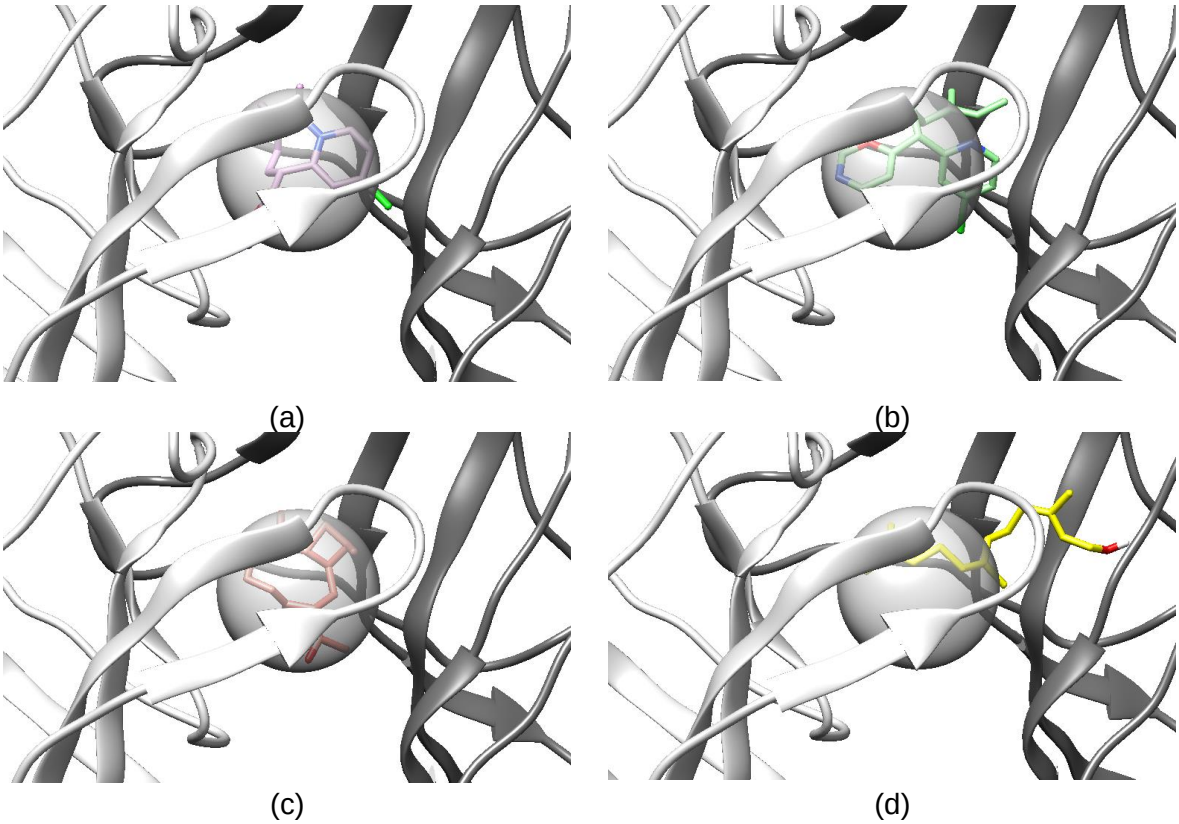

Figure 3. Comparative binding poses of DZP and ligands within the $GABA_A$ receptor (PDB: 6D6U). The receptor is visualized with chain D (α_1 subunit) in light gray and chain E (γ_2 subunit) in dim gray ribbon representation. A semi-transparent gray sphere (4 Å radius) denotes the center of Binding Site D, serving as a spatial reference for ligand localization. (a) DZP (realigned crystal pose from PDB 6X3X); (b) DZP (docked pose); (c) β-Caryophyllene acetate; (d) Farnesol.

3.4. Pilot Sleep Evaluation of Cutoff-Passing Fragrance Compounds

To evaluate the impact of fragrance compounds on sleep quality, we analyzed two key metrics—sleep latency and sleep efficiency—across experimental conditions. Out of the 132 fragrance compounds screened, anethole and vanillin were not necessarily the top-scoring docking candidates, but were instead selected for their favorable binding profiles within the cutoff and their olfactory acceptability as user-friendly, non-intrusive scents suitable for human exposure. It is important to note that the sleep evaluation was conducted in a limited format, primarily to provide preliminary biological context for the computational screening protocol, which remains the central focus of this study. Table 1 summarizes the molecular docking characteristics of these compounds, including centroid distance to the binding site's reference point, predicted binding affinity, and the percentage of interacting residues that overlapped with those of the reference ligand.

Table 1. Docking outcomes of selected fragrance compounds.

Fragrance Compound	Binding Site	Centroid Distance (Å)	Binding Affinity (kcal/mol)	Residue Similarity (%)
Anethole	G	0.56	-5.50	100
Vanillin	G	0.49	-4.62	100

As summarized in Table 2, participants exposed to vanillin showed an average sleep latency of 14 minutes and a sleep efficiency of 85%, compared to 35 minutes and 81%, respectively, under the no-fragrance control condition—reflecting a 21-minute reduction in latency and a 4-percentage-point increase in efficiency. Similarly, anethole was associated with a sleep latency of 21 minutes and a modest efficiency improvement to 84%. While derived from a limited-scale test, these results suggest that fragrance compounds selected through our docking-based cutoff framework may exhibit meaningful trends in sleep-related outcomes. This observation serves as a preliminary biological support to the computational protocol established in this study.

Table 2. Mean Sleep Latency and Efficiency by Fragrance Condition

Fragrance Compound	Mean Sleep Latency (min)	Mean Sleep Efficiency (%)
Control (no scent)	35	81
Anethole	21	84
Vanillin	14	85

4. Discussion

4.1. Fragrance Note Bias Reflects Binding Site Specificity

Analysis of olfactory note distribution among ligands passing the docking criteria revealed a clear bias toward certain scent profiles. Notes traditionally associated with warm and comforting olfactory experiences—including anisic (40%), smoky (38%), animalic (21%), food-like (22%), gourmand (20%), powdery, earthy, and spicy—were disproportionately represented among the ligands that met the cutoff criteria for Binding Site G. In contrast, cool-toned notes such as minty, marine, green, aldehydic, and citrus were notably underrepresented, with many registering at or near 0%. A distinct divergence was also observed between the two binding

sites. Ligands qualifying for Binding Site D predominantly exhibited animalic, musk, balsamic, and woody character—aromatic traits frequently associated with base notes in perfumery. These notes are known for their long-lasting nature and are often perceived as “skin-like” or subtly sensual by consumers.

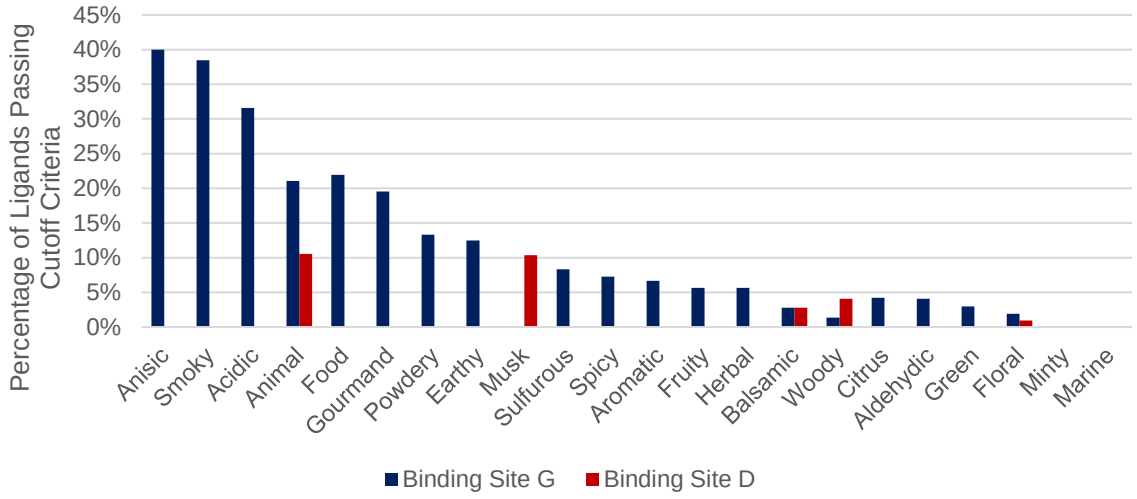

Figure 3. Proportional representation of olfactory notes among ligands binding to $GABA_A$ receptor sites. Distribution of olfactory note categories among ligands meeting the cutoff criteria for Binding Site G and Binding Site D of the $GABA_A$ receptor. Percentages represent the proportion of ligands with each note that qualified as candidates (i.e., met the spatial, energetic, and residue similarity thresholds) relative to all ligands with that note.

4.2. Neuropharmacological Validation of Docking-Derived Ligand Candidates

Intriguingly, the olfactory note analysis not only reveals correlations with fragrance profiles, but also resonates with established neuropharmacological findings. Notably, valerian essential oil, traditionally recognized for its sedative properties, was shown to significantly prolong pentobarbital-induced sleep time and enhance total sleep duration via inhalation in rodent models. This effect, as demonstrated by Komori et al. [18], was mediated through enhancement of GABAergic neurotransmission, specifically via inhibition of GABA transaminase activity, thereby elevating GABA levels in the brain. The major components of valerian essential oil—isovaleric acid and valeric acid—are classified under the “Acidic” olfactory note in the IFRA 2020 glossary and, according to our results, these molecules successfully passed the cutoff thresholds for Binding Site G, contributing to the 32% hit rate observed for the Acidic category (Figure 3). This direct alignment between molecular docking performance and empirical sleep enhancement provides a compelling biochemical rationale for the traditional use of valerian in sleep therapy. In a similar vein, anethole, a compound abundant in aromatic plants such as anise and fennel, met all cutoff criteria for Binding Site G. Recent literature by Khodadadian and Balali-Dehkordi [19] outlines the multifaceted neurological effects of anethole, highlighting its potential in modulating monoaminergic, GABAergic, and glutamatergic neurotransmission. The compound has been shown to exert anxiolytic, antidepressant, and anticonvulsant effects, with its therapeutic potential being attributed to both isomers—cis- and trans-anethole, contributing to the 40% hit rate observed for the Anisic category (Figure 3). These findings provide a robust pharmacological validation of our *in silico* screening protocol and support the hypothesis that ligands fulfilling our docking-based cutoff criteria may possess biologically relevant interactions with the $GABA_A$ receptor that translate into functional CNS effects.

5. Conclusion

This study was initiated with the hypothesis that fragrance molecules, through interaction with neurotransmitter receptors, may modulate mental calmness and improve sleep quality. Drawing upon prior evidence from neuropharmacological literature and reports from related institutions, we set out to systematically explore the olfactory–neurological interface using an integrative screening framework. Specifically, we focused on the $GABA_A$ receptor, a central mediator of inhibitory neurotransmission, and virtually screened 1,925 aroma chemicals at two of its primary ligand-binding domains: the endogenous GABA site (Binding Site G) and the benzodiazepine (DZP) site (Binding Site D). Application of rigorously defined spatial, energetic, and residue-based cutoff criteria yielded 116 fragrance candidates for Binding Site G and 16 for Binding Site D, resulting in a final shortlist of 132 compounds with docking profiles analogous to those of native ligands.

Through this cheminformatics- and structure-based pipeline, we not only prioritized potential actives, but also observed notable enrichment of traditionally calming scent categories—such as anisic, smoky, and animalic—within the candidate pool. Certain molecules, including valerian-derived acids and anethole, were found to exhibit both high docking fidelity and prior empirical support for GABAergic modulation, underscoring the physiological plausibility of our virtual screening method.

However, we fully acknowledge the limitations inherent in this study. First, ligand docking proximity to a binding site, while informative, does not equate to functional receptor modulation. Confirming true pharmacological efficacy will require future investigations using advanced molecular dynamics simulations or electrophysiological validation, such as patch-clamp techniques. Second, the human sleep evaluation component was intentionally limited in scope and sample size, conducted not as a clinical trial but as a pilot effort to provide preliminary biological context to the computational findings. Third, we recognize the importance of future work to identify and screen antagonistic or inverse agonist fragrance compounds—such as flumazenil analogs—which may interact differently with the receptor.

During this study, we also noted that the coordinate alignment between 6X3X and 6D6U structures—performed to allow direct comparison of DZP and GABA binding—was ultimately unnecessary, as the cryo-EM structure of 6X3X already contains both ligands co-bound. Nonetheless, this step reflects our methodological diligence and highlights the value of thorough structural assessment at the outset of computational modeling.

Despite these constraints, this work represents a novel convergence of fragrance chemistry, molecular pharmacology, and cosmetic innovation. It advances a data-driven approach to aromatherapy—an area often relegated to pseudoscience—by grounding it in quantifiable receptor-ligand interactions. By offering a reproducible protocol for fragrance-based neurotargeting, we hope this study lays the groundwork for future research and product development that integrates scent science with emotional and physiological wellness, ultimately contributing to more meaningful, evidence-based applications in the cosmetics and fragrance industries.

6. Acknowledgement

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