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In Silico Analysis of *Garcinia kola* Secondary Metabolites Targeting Dopamine and Norepinephrine Transporters for ADHD Therapy

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a neurological disorder associated with dysregulated dopaminergic and noradrenergic signaling. Although current pharmacotherapies are effective, they carry significant cardiovascular and abuse liabilities, highlighting the need for safer, targeted alternatives. This study evaluated *Garcinia kola* secondary metabolites as potential inhibitors of human dopamine (DAT) and norepinephrine (NET) transporters utilizing *in silico* approaches. Of twenty-seven metabolites, sixteen met Lipinski's Rule-of-Five and synthetic accessibility (SA) criteria and were further analyzed through molecular docking and CNS-relevant ADMET profiling. Cycloartenol, δ-tocotrienol, and 2-hydroxyxanthone demonstrated the strongest predicted dual-target binding affinities with both transporters, surpassing those of the reference ligand, atomoxetine, and engaging targets via hydrophobic, aromatic, and hydrogen-bonding interactions. ADMET analysis indicated that cycloartenol, δ-tocotrienol, and 2-hydroxyxanthone have high predicted brain exposure, favorable bioavailability, and no hepatotoxicity, whereas the reference ligand atomoxetine was flagged for hepatotoxicity. Garcifuran B and Garcipyran also showed favorable dual binding affinities and interactions, compared to the reference ligands, but predicted low blood-brain barrier permeability, suggesting that structural optimization may be required to improve their CNS delivery. In conclusion, δ-tocotrienol, cycloartenol, and 2-hydroxyxanthone emerge as predictive leads for dual DAT/NET inhibition and warrant further experimental *in vitro* and *in vivo* validation as safer, non-stimulant ADHD therapeutics.

Keywords: ADHD; Garcinia kola; molecular docking, dual inhibitors; dopamine transporter; norepinephrine transporter.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent neurodevelopmental condition characterized by hyperactivity, impulsivity, and inattention [1,2]. These symptoms are closely associated with dysregulated catecholaminergic signaling in the prefrontal cortex and striatal circuits, where the neurotransmitters dopamine (DA) and norepinephrine (NE) play pivotal roles [3]. The signaling of DA and NE is primarily terminated by their respective transporters, the dopamine transporter (DAT, SLC6A3) and the norepinephrine transporter (NET, SLC6A2). Both DAT and NET are 12-transmembrane-domain glycoproteins that mediate the sodium-chloride (Na+/Cl-)- dependent reuptake of neurotransmitters into presynaptic neurons [4,5]. By regulating synaptic monoamine levels, DAT and NET modulate signal termination and neurotransmitter recycling, thereby maintaining synaptic homeostasis, which is crucial for normal cognitive and motor functions [6,7].

Genetic and functional studies have implicated DAT and NET dysregulation in ADHD pathophysiology. A recent investigation found that the 5R/5R genotype and 5R allele of the intron-8 VNTR in the DAT1 gene increase the odds of ADHD in children and adolescents [8]. Neuroimaging in adult, drug-naive ADHD participants revealed significantly lower DAT availability in the bilateral nucleus accumbens [9]. The study also found a negative correlation between inattentive symptoms and DAT availability in the caudate [9]. Another PET study demonstrated reduced NET availability in right hemisphere attention networks in adults with ADHD [10]. These findings highlight DAT and NET as complementary therapeutic targets whose concurrent modulation may restore neurotransmitter balance more effectively than single-transporter inhibition.

Current ADHD medications, such as methylphenidate and atomoxetine, act on DAT and NET but present limitations, including cardiovascular side effects and abuse potential [11,12]. This has prompted a search for safer, naturally derived alternatives that can modulate dual transporters. The exploration of natural compounds as potential dual DAT/NET inhibitors represents a novel therapeutic direction that could improve efficacy while minimizing adverse effects.

Natural products have long served as reservoirs of bioactive compounds with therapeutic potential, especially in the search for novel central nervous system (CNS) agents. Among these, *Garcinia kola* (*Clusiaceae*), commonly known as bitter kola, stands out as a widely used ethnomedicinal species in West and Central Africa [13]. Phytochemical investigations of *Garcinia kola* have documented twenty-seven known secondary metabolites, including biflavonoids, polyisoprenylated benzophenones, xanthones, vitamin E derivatives, and sterols [13,14]. Some of these metabolites have prior pharmacological evidence relevant to CNS drug discovery. Biflavonoids and related constituents from *Garcinia kola*, particularly the Kolaviron complex of GB1, GB2, and several other metabolites, exhibit neuroprotective, antioxidant, and anti-inflammatory activities *in vitro* and *in vivo* [15-17]. Garcinol and Garcinoic acid have shown multi-target neuroprotective and anti-inflammatory effects [18].

Collectively, the reported neuroprotective, antioxidant, and anti-inflammatory properties of *Garcinia kola* metabolites suggest they may serve as CNS-active compounds for further investigation as modulators of dopamine and norepinephrine transporters implicated in ADHD. Despite prior work on *Garcinia kola* extracts, no systematic evaluation of *Garcinia kola* metabolites as dual DAT/NET inhibitors has been reported.

Recent advances in computational biology, including molecular docking and *in silico* ADMET profiling, have significantly accelerated the early stages of drug discovery [19]. These tools enable large-scale, cost-effective screening of natural product libraries against specific protein targets [19]. Docking algorithms predict high-affinity binding poses of chemicals (ligands) [20]. Concurrent ADMET analysis identifies lead candidates with favorable bioavailability, blood-brain barrier permeability, and minimal toxicity, therefore focusing downstream efforts on the most promising scaffolds [20].

Therefore, this study aims to identify natural dual DAT/NET inhibitors from Garcinia kola as potential leads for safer, more effective ADHD therapeutics.

2. Materials and Methods

2.1. Ligand preparation.

All twenty-seven known secondary metabolites of *Garcinia kola* were compiled from literature and retrieved as canonical SMILES from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) [13]. For compounds absent in PubChem, SMILES were generated from IUPAC names using the OPSIN tool [21-24]. All SMILES were curated, validated, and prepared in a Jupyter environment using RDKit [25]. Three-dimensional conformers were generated via the ETKDG algorithm, optimized with the Universal Force Field (UFF), and assigned Gasteiger charges. The optimized structures were then converted to PDBQT format.

2.2. Protein preparation.

Cryo-EM structures of the human norepinephrine transporter (NET, PDB ID: 8ZP2, 2.40 Å) and dopamine transporter (DAT, PDB ID: 9EO4, 2.66 Å) were obtained from the protein data bank (https://www.rcsb.org) [26, 27]. Structures were converted from CIF to PDB using PyMOL (v3.1.4), and prepared in AutoDockTools 1.5.7 [28, 29]. Co-crystallized ligands, water molecules, and heteroatoms were removed. For DAT, chain B was also removed to retain the functional monomer. Polar hydrogens were added, non-polar hydrogens merged, and Kollman charges applied. Final receptor files were saved in PDBQT format for docking.

2.3. Pharmacokinetic and synthetic accessibility assessment.

Preliminary pharmacokinetic and drug-likeness assessments were performed using ADMETlab 3.0 (https://admetlab3.scbdd.com) to evaluate Lipinski's Rule of Five compliance and synthetic accessibility (SA) scores [30]. The canonical SMILES strings of the *Garcinia kola* metabolites were uploaded to the server, and results were generated using default prediction settings. Compounds with more than one Lipinski violation or Synthetic Accessibility (SA) score above 6 were excluded from further analysis.

2.4. Molecular docking between ligands and receptors.

Molecular docking of ligands that passed preliminary screening was performed using AutoDock Vina (v1.1.2) under a semi-flexible protocol in which the receptor was kept rigid while ligands were fully rotatable [31]. For DAT, the grid box dimensions were 29 × 25 × 27 Å, centered at x = 134, y = 127, z = 130. For NET, the box dimensions were 22 × 27 × 29 Å, centered at x = 130, y = 126, z = 126. In both cases, the exhaustiveness parameter was set to

10, the number of output binding modes was fixed at 9, and the energy-range cutoff was set to 4.0 kcal/mol. The native co-crystallized ligands, cocaine (DAT) and atomoxetine (NET), were used as control ligands and re-docked using identical grid coordinates and parameters. The best docked poses were superimposed on their crystallographic conformations to compute RMSD values for heavy atoms in PyMOL. Validation was considered successful when RMSD values were below 2.0 Å, confirming the reliability of the docking protocol. Predicted binding affinities were then compared with those of the control ligands; in this context, a more negative binding energy indicated a stronger predicted ligand-receptor interaction.

2.5. ADME and toxicity prediction.

Post-docking pharmacokinetic and toxicity screening was performed using pkCSM (https://biosig.lab.uq.edu.au/pkcsm) and SwissADME [32,33]. Canonical SMILES for each ligand were submitted to the server, and predicted endpoints included blood-brain barrier permeability (log BB), Bioavailability, and Hepatotoxicity. Ligands were regarded as having acceptable ADMET profiles if bioavailability ≥ 0.55, log BB > 0.3, and predicted no hepatotoxicity.

2.6. Data analysis.

Docking results were visualized in BIOVIA Discovery Studio 2025 Client. Two-dimensional interaction diagrams of the best-scoring ligand-receptor complexes were generated [34].

3. Results and Discussion

3.1. Physicochemical profiles.

Lipinski's Rule of Five compliance was evaluated using molecular weight (≤ 500 Da), LogP (≤ 5), H-bond donors (≤ 5), and H-bond acceptors (≤ 10), while synthetic accessibility (SA) scores assessed ease of synthesis. As shown in Table 1 below, the *Garcinia kola* metabolites predicted diverse drug-likeness profiles. Of the 27 compounds analyzed, 10 met all Lipinski criteria, 6 showed 1 violation, and 14 predicted 2 or more violations. Applying a threshold of ≤ 1 violation and SA ≤ 6, sixteen metabolites (59%) were retained for further analysis.

Table 1. Predicted physicochemical parameters of *Garcinia kola* secondary metabolites.

Name	MW (Da)	HBA	HBD	TPSA (Å²)	nRotB	logP	Lipinski Violation	SA
Gb1	558.12	11	7	194.21	3	2.56	3	4.234
Gb2	574.11	12	8	214.44	3	2.26	3	4.331
Kolaflavanone	588.13	12	7	203.44	4	2.65	3	4.305
Garcinianin	556.10	11	7	198.12	3	3.69	3	3.851
Amentoflavone	538.09	10	6	181.80	3	4.62	2	3.038
Volkensiflavone	540.11	10	6	177.89	3	4.24	2	3.767
Morelloflavone	556.10	11	7	198.12	3	3.79	3	3.867
Kolanone	502.31	4	2	74.60	10	7.28	2	3.861
Garcinol	602.36	6	3	111.90	10	6.07	2	5.558
Garcinoic Acid	**426.28**	**4**	**2**	**66.76**	**10**	**6.60**	**1**	**3.656**
δ-Tocotrienol	**396.30**	**2**	**1**	**29.46**	**9**	**8.05**	**1**	**3.579**
Cycloartenol	**426.39**	**1**	**1**	**20.23**	**4**	**5.72**	**1**	**5.378**
24-Methylenecycloartenol	512.44	1	0	9.23	7	7.57	2	5.641
2-Hydroxyxanthone	**212.05**	**3**	**1**	**50.44**	**0**	**2.67**	**0**	**1.854**

Name	MW (Da)	HBA	HBD	TPSA (Å²)	nRotB	logP	Lipinski Violation	SA
4-Hydroxyxanthone	**212.05**	**3**	**1**	**50.44**	**0**	**2.87**	**0**	**1.923**
1,5-Dihydroxyxanthone	**228.04**	**4**	**2**	**70.67**	**0**	**2.53**	**0**	**2.215**
2-Hydroxy-1-Methoxyxanthone	**242.06**	**4**	**1**	**59.67**	**1**	**2.43**	**0**	**2.118**
3-Hydroxy-4-Methoxyxanthone	**242.06**	**4**	**1**	**59.67**	**1**	**2.43**	**0**	**2.086**
2,5-Dihydroxy-1-Methoxyxanthone	**258.05**	**5**	**2**	**79.90**	**1**	**1.79**	**0**	**2.390**
2-Hydroxy-1,8-Dimethoxyxanthone	**272.07**	**5**	**1**	**68.90**	**2**	**2.04**	**0**	**2.311**
1,3,5-Trihydroxy-2-Methoxyxanthone	**274.05**	**6**	**3**	**100.13**	**1**	**1.73**	**0**	**2.518**
1,2-Dimethoxyxanthone	**256.07**	**4**	**0**	**48.67**	**2**	**2.31**	**0**	**1.967**
Gakolanone	518.30	5	4	97.99	12	8.47	2	3.290
Garcifuran A	**286.08**	**5**	**2**	**72.06**	**3**	**2.75**	**0**	**2.300**
Garcifuran B	**256.07**	**4**	**2**	**62.83**	**2**	**2.81**	**0**	**2.214**
Garcinal	**410.28**	**3**	**1**	**46.53**	**10**	**7.41**	**1**	**3.762**
Garcipyran	**314.12**	**5**	**3**	**79.15**	**3**	**2.92**	**0**	**3.169**

[1] Compounds with bolded values fulfil Lipinski's rule of five; [2] MW: Molecular Weight; HBA: Number of Hydrogen Bond Acceptors; HBD: Number of Hydrogen Bond Donors; TPSA: Total Polar Surface Area; nRotB: Number of Rotatable Bonds; logP: Octanol-Water Partition Coefficient; SA: Synthetic Accessibility Score.

The Xanthone derivatives (i.e, 2-hydroxyxanthone, 4-hydroxyxanthone, 1,5-dihydroxyxanthone) uniformly occupied the "sweet spot" of drug-likeness, with molecular weights of 212-228 Da, no Lipinski violations, Log P values between 1.7 and 2.9, and synthetic accessibility scores < 3. According to Veber *et al*., compounds with TPSA ≤ 140 Å² and ≤ 10 rotatable bonds exhibit high permeability and bioavailability [35]. Notably, the xanthones in our selection meet these criteria, positioning them as promising leads with potential for high permeability and bioavailability.

In contrast, the flavonoid-type biflavonoids like Gb1, Gb2, Kolaflavanone, and Morelloflavone were predicted to have multiple Lipinski violations, primarily due to high molecular weights (>550 Da), their large number of hydrogen bond donors and acceptors, and polar surface areas exceeding 180 Å². Despite these, their moderate LogP values (~ 2.5-4.5) and acceptable SA scores suggest they may still be suitable for non-oral or modified delivery approaches [36].

Highly lipophilic compounds such as δ-tocotrienol, garcinol, and gakolanone (LogP > 6) posed solubility and metabolic concerns. Gakolanone, with the highest LogP (8.47) and 12 rotatable bonds, represents an extreme case in which hydrophobicity and molecular flexibility may limit absorption and metabolic stability [33, 34]. Such compounds may suffer from poor dissolution, reduced permeability, and rapid cytochrome P450-mediated clearance [37].

3.2. Molecular docking between ligands and receptors.

Molecular docking was performed to determine the binding affinity and interactions of selected *Garcinia kola* metabolites with NET and DAT. Molecular docking is a predictive tool for evaluating ligand-receptor complementarity by estimating free binding energy and identifying key residues involved in molecular recognition [38]. In this case, lower (more negative) docking scores indicated stronger predicted affinities and more stable complexes.

Among the sixteen *Garcinia kola* metabolites, cycloartenol and δ-Tocotrienol exhibited the most favorable predicted binding affinities, exceeding those of the reference ligands. In NET, Cycloartenol showed the lowest binding energy (-11.3 kcal/mol) compared to

atomoxetine (-8.6 kcal/mol), the reference ligand, followed by δ-Tocotrienol (-10.1 kcal/mol). In DAT, δ-Tocotrienol exhibited the most favorable binding (-10.7 kcal/mol), surpassing cocaine (-9.0 kcal/mol), with cycloartenol (-9.7kcal/mol) again ranking among the top-scoring compounds. Other metabolites, including Garcifuran B, Garcipyran, and Garcinoic acid, showed stronger affinities than the reference ligands, though slightly lower than cycloartenol and δ-Tocotrienol.

Redocking the crystallized ligands confirmed the accuracy of the docking setup. Atomoxetine in NET and cocaine in DAT reproduced their original binding poses with RMSD values of 0.416 Å and 0.87 Å and docking scores of -8.6 kcal/mol and -9.0 kcal/mol, respectively. These results show that the docking method was reliable for further comparison. Binding energy values (kcal/mol) and interacting amino acid residues are summarized in Tables 2 and 3.

Table 2. Predicted binding energy of filtered *Garcinia kola* metabolites to DAT and NET.

Names	Binding affinity (kcal/mol)	
	NET	DAT
Garcinoic acid	-9.2	-9.9
δ-tocotrienol	-10.1	-10.7
Cycloartenol	-11.3	-9.7
2-hydroxyxanthone	-8.7	-9.5
4-hydroxyxanthone	-8.0	-8.5
1,5-dihydroxyxanthone	-8.0	-8.2
2-hydroxy-1-methoxyxanthone	-8.2	-8.4
3-hydroxy-4-methoxyxanthone	-7.6	-7.6
2,5-dihydroxy-1-methoxyxanthone	-7.9	-7.8
2-hyrdoxy-1,8-dimethoxyxanthone	-7.7	-8.1
1,3,5-trihydroxy-2-methoxyxanthone	-8.2	-8.5
1,2-dimethoxyxanthone	-7.7	-8.0
Garcifuran A	-8.3	-9.0
Garcifuran B	-9.5	-9.9
Garcinal	-9.4	-9.4

Table 3. Predicted interaction type and residues of top-scoring *Garcinia kola* metabolites to DAT and NET.

Receptors	Compound name	Hydrogen bonding	Hydrophobic interaction
8ZP2	Cycloartenol	-	TYR A:152, PHE A:72, VAL A:148, MET A:424, PHE A:317
	δ-Tocotrienol	-	PHE A:317, ALA A:77, TRP A:80, ALA A:477, VAL 148, TYR152
	Garcifuran B	ASP75, ALA73, GLY423, SER318	TYR A:152, PHE A:72, PHE A:317, VAL A:148, PHE A:317
	Garcinal	SER420, GLY478	VAL A:148, TYR A:152, ALA A:77, PHE A:317
	Garcipyran	PHE72	VAL A:148, PHE A:317, ASP A:473, TYR A:152
	2-Hydroxyxanthone	SER419	PHE A:72, TYR A:152, VAL A:148, GLY A:423, PHE A:317, ASP A:75
	Atomoxetine (Native Ligand)	ALA A:73, PHE A:72	VAL A:148, TRYA:152, ALA A:477
9E04	Cycloartenol	-	PHE B:326, TYR B:156, VAL B:152, ALA B:423
	δ-Tocotrienol	ALA B:423	TRP B:84, ILE B:390, ALA B: 81, TYR B:156, PHE76, VAL152, PHE326
	Garcifuran B	PHE B:76, ALA B:77, GLY B:426, PHE B:320	ALA B:423, PHE B:326, TYR B:156, VAL B:152, ASP B:79
	Garcinal	MET B:427, SER B:149	TYR B:156, VAL B:152, PHE B:326, ALA B:480, PHE B:320, ARG B:85

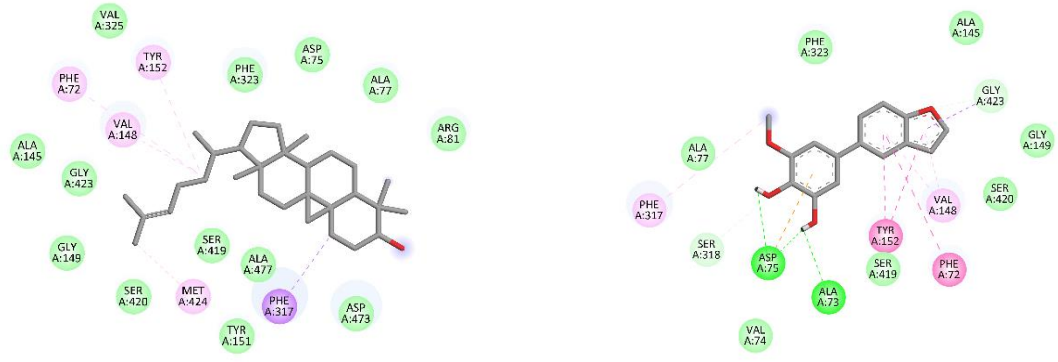
Receptors	Compound name	Hydrogen bonding	Hydrophobic interaction
	Garcipyran	ALA B:77, PHE B:76, ASN B:157, SER B:419	TYR156, PHE326, VAL152, ALA423, MET B:427, VAL B:430
	2-Hydroxyxanthone	-	PHE B:76, PHE B:326, TYR B:156, VAL B:152, GLY B:426, ALA B:423
	Cocaine (native ligand)	ASN B:82, ALA B:77	PHE B:326, PHE B:76, SER B:422, ALA B:423, VAL B:152

The substrate-binding (S1) pockets of DAT and NET are predominantly hydrophobic, lined with aromatic and aliphatic residues, such as Phe, Tyr, Val, Ile, and Leu. This environment favors non-polar interactions with ligands, though the pockets also contain polar residues that enable hydrogen bonding and ion coordination, which are important for substrate recognition and binding. Beyond binding energy values, the occurrence of similar interaction patterns, such as hydrogen bonds, hydrophobic interactions, and the engagement of specific amino acid residues, indicates comparable ligand-receptor activities [39].

Cycloartenol and δ-tocotrienol possess divergent chemotypes, which explain their complementary binding patterns. Cycloartenol has a polycyclic sterol structure with four fused rings and a largely hydrophobic branched hydrocarbon tail, bearing only a single 3β-hydroxyl group [40]. This provides a broad non-polar surface that interacts well with key aromatic and aliphatic residues in the binding sites of DAT and NET, via van der Waals and hydrophobic contacts. These extensive hydrophobic interactions explain cycloartenol's strong affinity toward DAT and NET.

In contrast, δ-tocotrienol features a polar chromanol head group that carries a phenolic hydroxyl and an aromatic ring capable of forming hydrogen bonds. Extending from this head is a flexible unsaturated isoprenoid tail containing three trans-double bonds [41]. This tail can assume various conformations within the binding pocket and interacts with both aromatic and aliphatic residues through π-alkyl and hydrophobic contacts. Thus, δ-tocotrienol combines polar interactions via hydrogen bonds with hydrophobic/π interactions, enabling complementary binding behavior.

Comparing the test ligands with the native ligands revealed substantial overlap in the residues engaged. In NET, both cycloartenol and δ-Tocotrienol formed exclusively hydrophobic contacts with residues such as Phe72, Tyr152, Val148, and Ala477, which were also interacted with by the native ligand, atomoxetine. Garcifuran B, in contrast, formed hydrogen bonds with Ala73, a key residue also bonded by atomoxetine, and displayed additional π-π interactions, indicating a mixed binding mode that mimics atomoxetine. These interactions with NET are illustrated in Figure 1.



(a) **(b)**

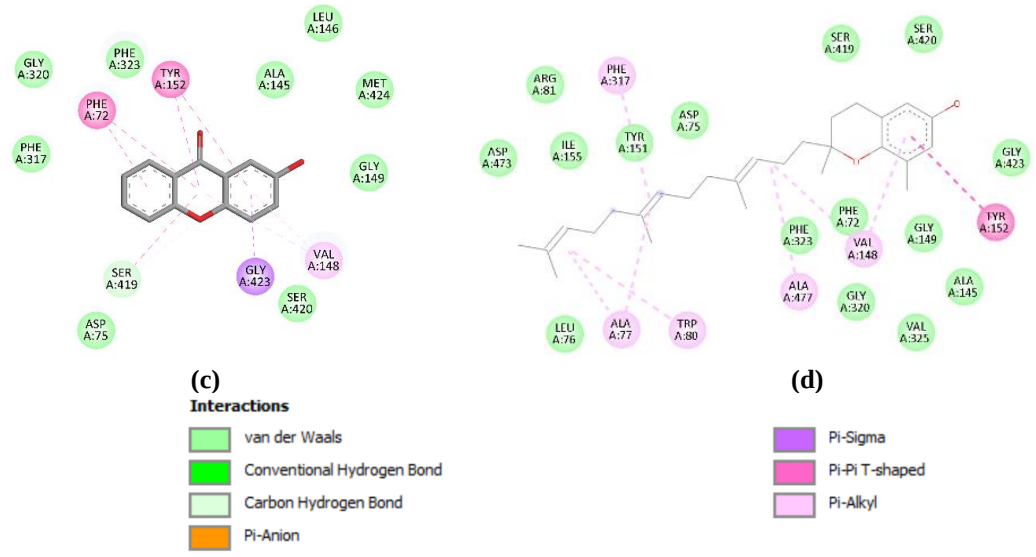
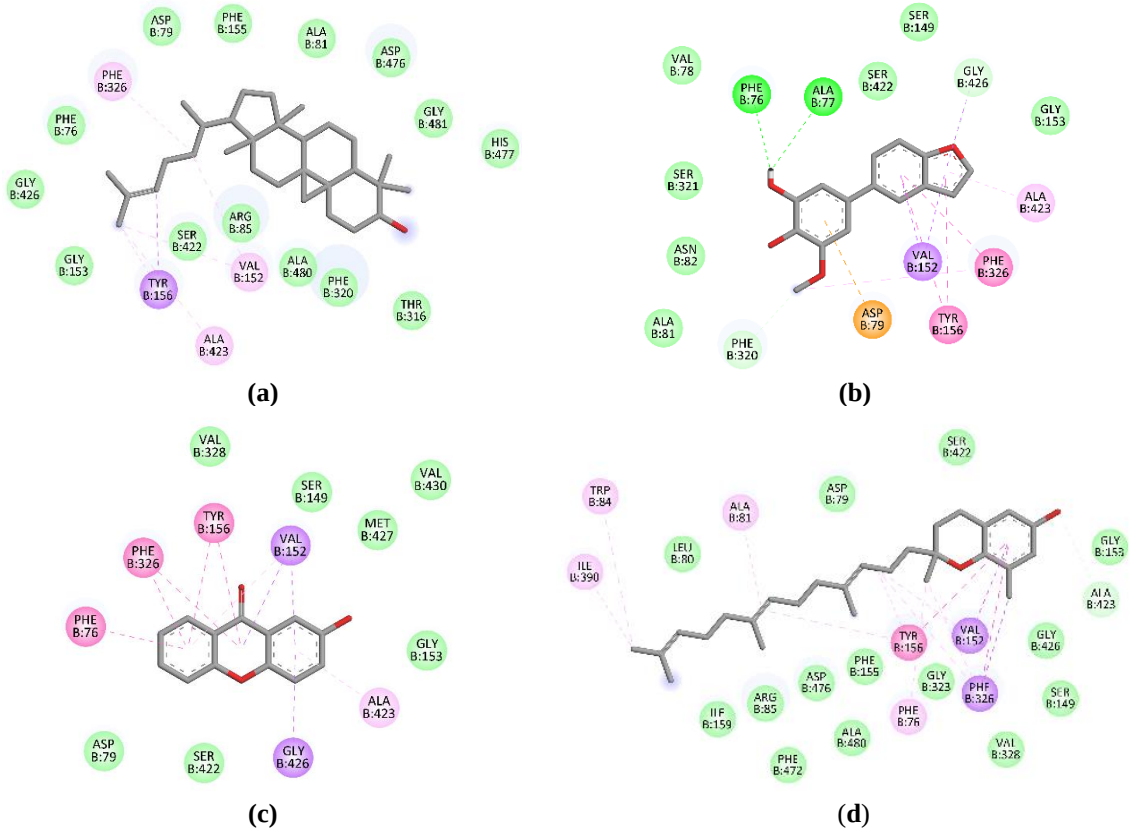


Figure 1. Two-dimensional interaction diagrams of some *Garcinia kola* metabolites docked with NET. **(a)** Cycloartenol with NET; **(b)** Garcifuran B with NET; **(c)** 2-Hydroxyxanthone with NET; **(d)** δ-tocotrienol with NET.

In DAT, Cycloartenol interacted with five of the seven residues that cocaine binds to, though also with purely hydrophobic interactions. δ-Tocotrienol showed a similar hydrophobic interaction but also formed a weak carbon-hydrogen bond with Ala423 via its hydroxyl (-OH) group. Garcifuran B (-9.9 kcal/mol) also showed a robust interaction profile with DAT, involving multiple hydrophobic and hydrogen-bond interactions, including a hydrogen bond with Ala77, as observed with the native ligand, cocaine. These interactions with DAT are illustrated in Figure 2.



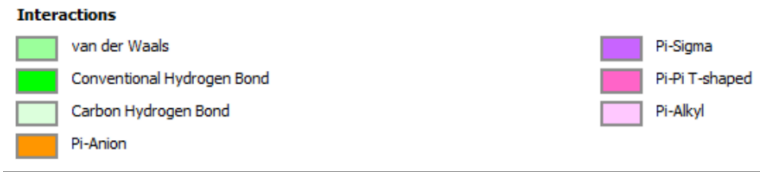


Figure 2. Two-dimensional interaction diagrams of some *Garcinia kola* metabolites docked with DAT. **(a)** Cycloartenol with DAT; **(b)** Garcifuran B with DAT; **(c)** 2-Hydroxyxanthone with DAT; **(d)** δ-tocotrienol with DAT.

Other compounds, including Garcipyran and 2-hydroxyxanthone, also predicted docking affinities exceeding those of reference ligands.

Taken together, our results highlight two distinct binding strategies among the top-scoring phytochemicals. Ligands such as cycloartenol and δ-Tocotrienol achieved exceptional docking scores by dense hydrophobic and aromatic interactions, whereas compounds such as Garcifuran B, Garcinal, and Garcipyran combined extensive π-stacking with directional hydrogen bonds.

3.3. CNS-relevant ADME and toxicity profiles.

Transitioning from binding potency to drug candidacy requires ADME (Absorption, Distribution, Metabolism, Excretion) properties and toxicity evaluation, especially for Central Nervous System (CNS) targets. The reference compound used for this ADMET study was atomoxetine, a clinically approved norepinephrine reuptake inhibitor used in the management of ADHD [42]. It served as a pharmacological benchmark for evaluating both brain permeability and systemic safety among the *Garcinia kola*-derived metabolites. We conducted thorough ADMET analysis after molecular docking of the selected bioactive compounds, which showed more negative binding affinity than our reference compound. Blood-brain barrier (BBB) permeability was considered acceptable when log BB exceeded 0.3; compounds with a bioavailability score of 0.55 or higher and no predicted hepatotoxicity were regarded as desirable. Metabolites meeting these criteria were prioritized as potential dual DAT/NET inhibitors. The key ADME and toxicity parameters for each compound are summarized in Table 4.

Table 4. Predicted ADME and toxicity properties of some filtered *Garcinia kola* secondary metabolites.

Compound	BBB (log BB)	Bioavailability	Hepatotoxicity
Cycloartenol	0.794	0.55	No
δ-tocotrienol	0.696	0.55	No
2-Hydroxyxanthone	0.330	0.55	No
Garcinal	-0.079	0.55	No
Garcifuran B	-0.049	0.55	No
Atomoxetine (Control)	0.741	0.55	Yes

Comparing the ADMET predictions of these natural compounds to those of atomoxetine provided insight into how their pharmacokinetic and toxicological profiles might influence their potential as dual dopamine and norepinephrine transporter inhibitors.

Good bioavailability and efficient brain penetration are key factors that determine whether a compound can reach and sustain adequate concentrations at its target sites within the central nervous system [43,44]. According to previous studies, compounds with a bioavailability score of ≥ 0.55 and log BB > 0.3 are predicted to have a high likelihood of crossing the blood-brain barrier and penetrating the brain parenchyma [44, 45]. In this context, cycloartenol and δ-tocotrienol showed particularly high bioavailability values of 0.55 and log

BB values of 0.794 and 0.696, respectively. These findings suggest that both compounds could achieve substantial systemic and brain effects similar to those of atomoxetine. Such high permeability complemented their strong docking affinities at both DAT and NET binding sites. Together, these results support their ability to bind and interact effectively with transporter proteins in the CNS, strengthening the argument for their possible dual inhibitory function.

The toxicity predictions also offer meaningful insight when viewed alongside atomoxetine. While atomoxetine was predicted to be hepatotoxic, consistent with reports of rare idiosyncratic liver injury during clinical use, none of the *Garcinia kola* metabolites were flagged as hepatotoxic [46]. This suggests a potentially safer hepatic profile, which is an encouraging outcome for the natural product-derived candidates.

2-Hydroxyxanthone exhibited favorable pharmacokinetic and safety properties, consistent with its strong predicted dual-target binding at both DAT and NET. Garcifuran B and Garcinal also demonstrated relatively balanced pharmacokinetic and safety profiles, with high bioavailability, and no predicted hepatotoxicity. However, their log BB values (-0.049 for Garcifuran B and -0.067 for Garcinal) suggest limited brain penetration compared to cycloartenol and δ-tocotrienol. Despite this limitation, their lower predicted toxicity makes them potential leads that require further structural optimization to improve CNS delivery.

Overall, the combined analysis of docking and ADMET data provided strong support for the dual-inhibitor hypothesis. Both cycloartenol and δ-Tocotrienol showed complementary high-affinity binding to dopamine transporter (DAT) and norepinephrine transporter (NET), suggesting the potential for simultaneous modulation of these critical monoaminergic pathways. In addition, their predicted pharmacokinetic profiles indicate favorable ADMET characteristics, which could facilitate sufficient penetration into the central nervous system.

4. Conclusions

This *in silico* investigation identified cycloartenol, δ-Tocotrienol, and 2-Hydroxyxanthone as promising *Garcinia kola*-derived scaffolds with dual inhibitory potential against the dopamine transporter (DAT) and norepinephrine transporter (NET). These compounds demonstrated binding affinities and ADMET properties superior to the established drug atomoxetine. While these findings are encouraging, it is important to emphasize that they are based solely on computational predictions. Therefore, comprehensive *in vitro* assays and *in vivo* studies will be necessary to confirm whether these compounds can effectively inhibit transporter activity and produce meaningful pharmacological effects in the brain. In addition, further structural optimization of Garcinal and Garcifuran B is needed to improve their blood-brain barrier permeability.

Author Contributions

Conceptualization, O.E.C. and O.E.; methodology, O.E.C., O.E., and I.C.N.; software, O.E.C., M.E.O., and I.C.N.; validation, O.E.C., O.E., M.E.O., and R.M.A.; formal analysis, O.E.C., I.C.N., M.E.O., and S.W.A.; data curation, O.E.C., R.M.A., and S.W.A.; writing—original draft preparation, O.E.C., M.E.O., and S.W.A.; writing—review and editing, O.E.C., O.E., I.C.N., and R.M.A.; visualization, O.E.C., I.C.N., and S.W.A.; supervision, O.E.C.; project administration, O.E.C. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

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