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Predicting the biological activity of selected phytochemicals in *Alsophila spinulosa* leaves against 4-aminobutyrate-aminotransferase: A potential antiepilepsy agents

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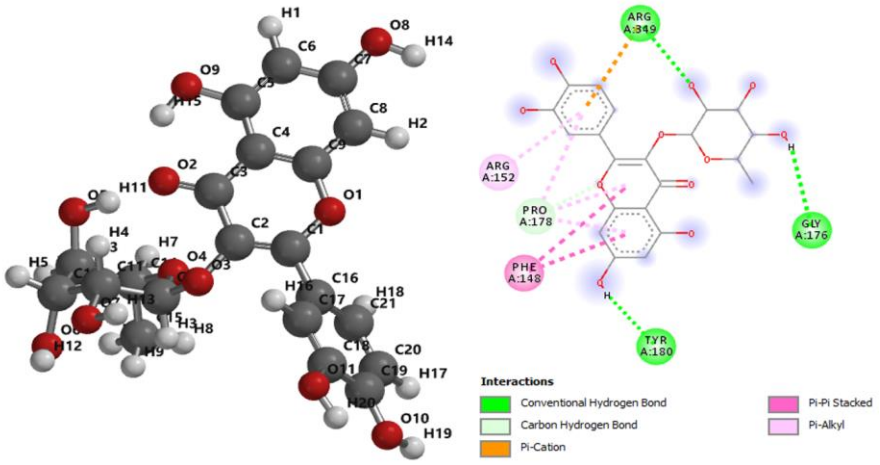
Abstract

The use of medicinal plants as an alternative mean of treating various diseases has drawn the attention of several researchers. The desire to find lasting solutions to epilepsy among humans increases every day. Thus, this work was aimed at investigating the potential capacity of the studied phytochemicals in *Alsophila spinulosa* against human 4-aminobutyrate-aminotransferase as well as to predict the nonbonding interactions involved in the studied complexes. In this work, ten compounds with biological activities were selected and studied using molecular docking method. The molecules selected obtained from *A. spinulosa* leaves were optimized and various descriptors that described the anti-4-aminobutyrate-aminotransferase features were obtained. More so, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (compound 9) with highest binding affinity proved to have greater strength to inhibit 4-aminobutyrate-aminotransferase thereby downregulating epilepsy than other studied compounds and the reference drug (clobazam). The ADMET features of both compound 9 and clobazam were explored and reported.



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5. herbs.

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Highlights

- The descriptors that enhance the inhibiting activity of the studied ligands were observed.
- The amino acid residues involved in the interaction were investigated.
- Pharmacokinetic analysis on the ligand with highest binding affinity was examined.

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1. Introduction

Traditional medicine has played a crucial role in boosting human health for years (Kebede *et al.*, 2021). Many ground-breaking successes in recent therapeutic science depend greatly on natural/local resources (Shriram *et al.*, 2018; Poulakou *et al.,* 2018). Over the years, many medicinal agents of synthetic and natural products have been used to combat diseases and infections (Pitout 2008). The World Health Organization reports that more than 60% of developing countries still use herbal drugs originating from medicinal plants as alternative medicine (Duraipandiyan *et al.*, 2006; Mishra *et al.*, 2013; Vaou *et al.*, 2021).

One of the most common neurological syndromes in the world is epilepsy, which remains in third position among the diseases that affect people with old age (Hirtz *et al.*, 2007; Werhahn 2009; Queeny *et al.*, 2018; Dunkel *et al.,* 2023). Its rate of increase has been observed to be high in infants and aged people (Hesdorffer *et al.*, 2011; Jeżowska-Jurczyk *et al.*, 2023). As stated by Gagliano *et al.* (2018), more than 45 million people have been reported to have epilepsy. Antiepileptic agents are one way of combating epilepsy; nevertheless, the activities of epilepsy in 80% of patients remain unrestrained. The tactics behind the treatment failure of epilepsy still seem to be unclear; however, the fight against epilepsy by scientists all over the world has been observed to be increasing (Kwan and Brodie, 2000; Bartolini *et al.*, 2023). According to Mukhopadhyay *et al.* (2012), epilepsy is a combination of many syndromes, each of which has various warning signs such as intermittent irregular electrical activity in the brain.

Gamma-aminobutyrate-aminotransferase played a significant role in the degradation of the inhibitory neurotransmitter. It has been the target of several antiepileptic drug-like compounds (Choi and Churchich, 1986). 4-Aminobutyrate-aminotransferase was observed to have the ability to transfer nitrogenous groups and catalyze the combination of 4-aminobutanoate and 2-oxoglutarate, resulting in succinate semialdehyde and L-glutamate (Shen *et al.*, 2023; Kim and Yoon, 2023; Zhang *et al.,* 2022; Gao *et al.,* 2022; Yasuhide *et al.,* 1999).

Alsophila spinulosa is a plant with much biological importance. According to Morton (1971), it is a fern that looks like a tree. It grows in humus soil and can be found in countries such as China, Japan, and India. In China, it is used to treat various ailments, including rheumatism, helminthic infections, cough, and gout (Abbas *et al.*, 2016). More so, in American continents, it is used in teas and as poultices for treating some ailments (Irene *et al.*, 2023).

It belongs to the Cyatheaceae family and is commonly called the flying spider-monkey tree fern (Chiang *et al.*, 1994; Lanza *et al.*, 2022). The trunk of *A. spinulosa* can grow taller than 5 m (Chinese DmgDictionay, 1985; Yan *et al.*, 2022). It is a fern and it possesses the potential ability to inhibit tumors (Kan, 1986).

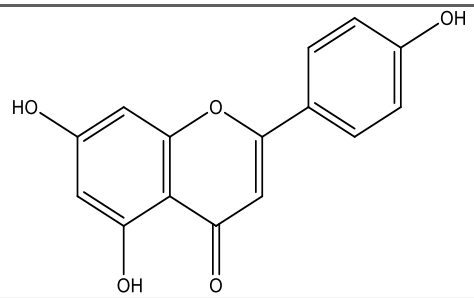
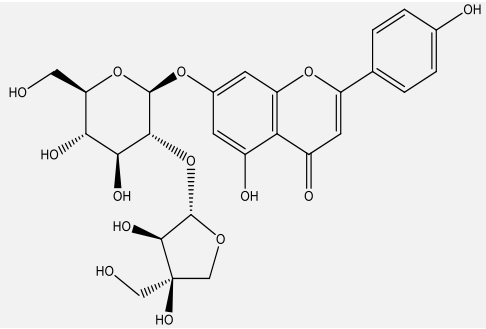
Therefore, this work aims to evaluate the potential inhibitory properties of selected phytochemicals present in *A. spinulosa* against human 4-aminobutyrate-aminotransferase and investigate the potential nonbonding interaction involved in the studied complexes and their efficiency.

2. Methodology

2.1 Software and hardware

The optimization of the studied compounds was accomplished using density functional theory via Spartan '14 software (Semire *et al.,* 2017). The binding affinity and nonbonding interactions between selected phytochemicals in *A. spinulosa* leaves and 4-aminobutyrate-aminotransferase were investigated via docking study using Pymol for treating enzyme, Discovery Studio software for viewing the interaction between the docked complexes, AutoDock tool for locating a binding site in the studied protein and AutoDock Vina software for docking calculation. The names and the two-dimensional structures of the selected phytochemicals are shown in **Table 1**.

Table 1. Studied phytochemicals obtained from *A. spinulosa.*

	Structures	IUPAC Names
1		5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one
2		7-(((2S,3R,4S,5S,6R)-3-(((2S,3R,4R)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)oxy)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-5-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one

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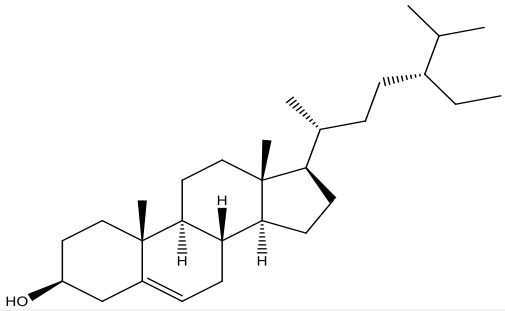
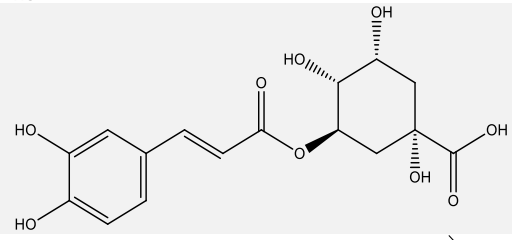
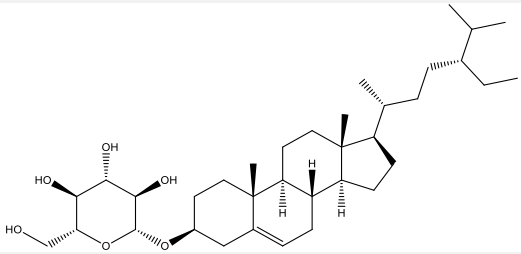
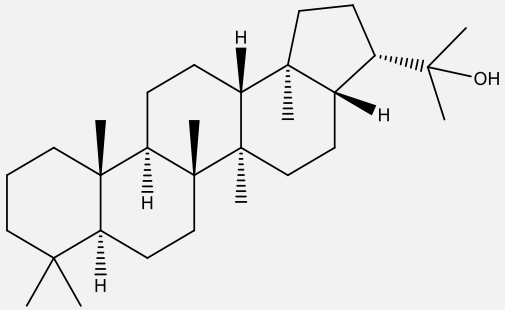
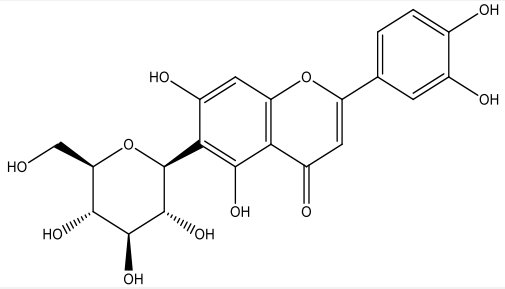
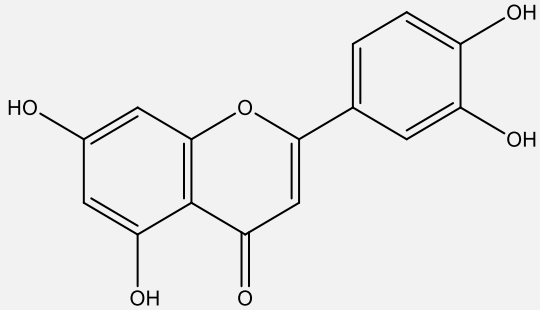
3		(3S,8S,9S,10R,13R,14S,17R)-17-((2R,5R)-5-ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol
4		(1S,3R,4R,5R)-3-(((E)-3-(3,4-dihydroxyphenyl)acryloyl)oxy)-1,4,5-trihydroxycyclohexanecarboxylic acid
5		(2R,3R,4S,5S,6R)-2-(((3S,8S,9S,10R,13R,14S,17R)-17-((2R,5R)-5-ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol
6		2-((3S,3aS,5aR,5bR,7aS,11aS,11bR,13aR,13bS)-5a,5b,8,8,11a,13b-hexamethylicosahydro-1H-cyclopenta[a]chrysen-3-yl)propan-2-ol
7		2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-4H-chromen-4-one
8		2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one

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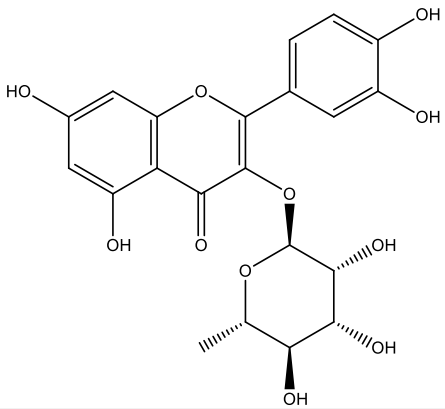
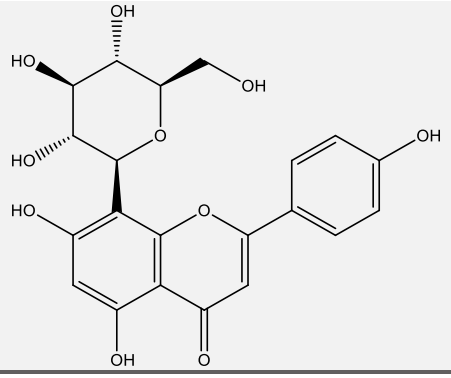
9		2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one
10		5,7-dihydroxy-2-(4-hydroxyphenyl)-8-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-4H-chromen-4-one

Source: Retrieved from Storici *et al.*, (2004).

2.2. Receptor (target)

The studied receptor (4-aminobutyrate-aminotransferase with protein data bank code: 1OHV) used in this work was repossessed from the recognized database (protein data bank) (Storici *et al.*, 2004).

2.3. Studied pharmacophore

Ten pharmacophores from *A. spinulosa* leaves were selected and prepared for a molecular docking study (Chen *et al.,* 2008). The selected compounds were chosen based on descriptions from literature (Vijayakumar *et al.*, 2018) and the compounds were obtained from a recognized database (https://pubchem.ncbi.nlm.nih.gov/).

2.4. Studied protein preparation

The studied receptor was retrieved from a protein data bank and a series of small molecules such as acetate ion (ACT), pyridoxal-5'-phosphate (PLP) and FE_2/S_2 (inorganic) cluster (FES) as well as water molecules were downloaded with it. The necessary factors for the downloaded receptor (resolution, R-value free, and R-value work) were observed to be 2.30, 0.221 and 0.118 Å, respectively. The studied receptor was treated using Pymol v 1.7.4 software and both small molecules such as ACT, PLP and FES as well as water molecules were removed and saved the clean 4-Aminobutyrate-Aminotransferase in .pdb format (El Fadili *et al.*, 2022a; Erazua *et al.*, 2023). The binding site in clean/treated 4-aminobutyrate-aminotransferase (PDB ID:1ohv) was predicted using AutoDockTools-1.5.6 (Waziri *et al.*, 2023; El Fadili *et al.*, 2022b). The calculation and analysis of site map of the studied receptor revealed the likely binding site and the figure for center (center_x = 5.638; center_y = 3.578 and center_z = 21.309) as well as the size of the site area (size_x = 62; size_y = 62 and size_z = 84) were reported accordingly. The docking calculation was executed using AutoDock Vina software to calculate binding affinity between the studied complexes.

2.5. ADMET investigation

This study was executed using ADMETsar 2.0 online software (Oyebamiji *et al.*, 2022). The ligands with higher binding affinity were investigated and absorption, distribution, metabolism, excretion, and toxicity (ADMET) factors such as physicochemical property, medicinal chemistry, absorption, distribution, metabolism, excretion, toxicity, environmental toxicity, tox21 pathway, and toxicophoric rule were considered.

3. Results and Discussion

3.1. Calculated descriptors

The descriptors obtained from optimization of the phytochemicals of *A. spinulosa* leaves revealed the activities of the studied medicinal plants. The descriptors obtained are reported in **Table 2**. According to Adeoye *et al.* (2022), the higher the highest occupied molecular orbital energy (E_{HOMO}), the better the tendency of the compound to release electrons to the nearby molecules. The unit for highest occupied molecular orbital energy was electron volt (eV) and as shown in **Table 2**, (1S,3R,4R,5R)-3-(((E)-3-(3,4-dihydroxyphenyl)acryloyl)oxy)-1,4,5-trihydroxycyclohexanecarboxylic acid (compound **4**) possess the potential strength to react better than other studied compounds. Also, the lower the lowest unoccupied molecular orbital energy (E_{LUMO}), the greater the strength of molecules to receive electrons from the compound that can give it out; thus, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (compound **9**) showed potential strength to receive electron from nearby compounds thereby brings about better interactions.

Other calculated descriptors (band gap, dipole moment, molecular weight (≤ 500 amu) ovality, log P (≤5), polarizability, hydrogen bond donor (HBD) (≤5) and hydrogen bond acceptor (HBA) (≤10)) are reported in **Table 2**.

Table 2. The selected descriptors obtained from *A. spinulosa* leaves.

	E_{HOMO} (eV)	E_{LUMO} (eV)	EG (eV)	DM (Debye)	MW (amu)	AREA (Å²)	OVA	LOG P	POL (Å³)	HBD	HBA
1	−6.06	−1.60	4.46	4.39	270.24	266.07	1.38	−2.38	60.79	3	5
2	−6.06	−1.64	4.42	12.60	564.49	517.78	1.69	−5.68	81.15	8	14
3	−6.16	0.71	6.87	2.11	414.71	493.59	1.63	8.14	79.85	1	1
4	−5.74	−1.60	4.14	2.03	354.31	350.48	1.54	−2.42	66.53	6	7
5	−6.21	0.69	6.90	5.94	576.85	628.71	1.77	6.40	90.98	4	6
6	−6.79	1.77	8.56	1.76	428.74	460.39	1.51	8.49	79.90	1	1
7	−5.87	−1.68	4.19	4.35	448.38	400.84	1.55	−6.39	72.21	8	11
8	−5.85	−1.64	4.21	7.55	286.23	273.50	1.39	−3.46	61.40	3	6
9	−5.86	−1.74	4.12	11.36	448.38	404.80	1.55	−5.68	72.50	7	11
10	−6.10	−1.67	4.43	5.06	432.38	384.94	1.50	−5.31	71.61	7	10

EG: Energy gap; DM: Dipole moment; MW: Molecular Weight; OVA: Ovality; LOG P: Lipophilicity; POL: Polarozability; HBD: Hydrogen bond donor; HBA: Hydrogen Bond Acceptor.

3.2. Molecular docking investigation

The docking of selected phytochemicals in *A. spinulosa* leaves was executed in 4-aminobutyrate-aminotransferase. Ten phytochemicals were docked into the active site of the 4-aminobutyrate-aminotransferase with PDB ID 1ohv and binding affinity, residue involved in the interactions as well as types of nonbonding interaction involved in the docked complexes were observed. The report obtained for studied docked complexes were: compound **1** (–33.472 kJ mol^{-1}; Lys442, Asp441, Asp415, Arg404, Met186, Arg222; conventional hydrogen bond, carbon hydrogen bond, pi-cation, pi-anion, pi-alkyl); compound **2** (–35.564 kJ mol^{-1}; Cys169, Phe161, Arg156, Pro178, Arg152, Arg349, Tyr180; conventional hydrogen bond, pi-cation, pi-sulfur, pi-pi stacked, pi-alkyl); compound **3** (–34.7272 kJ mol^{-1}; Lys145, Pro178, Trp215, Met149, Phe144, Phe148, Phe213, Cys177, Gly176; carbon hydrogen bond, alkyl, pi-alkyl); compound **4** (–32.6352 kJ mol^{-1}; Phe148, Arg349, Tyr180, Pro178, Arg156, Arg152, Gly176; conventional hydrogen bond, unfavorable donor-donor, pi-pi stacked, pi-alkyl); compound **5** (–33.472 kJ mol^{-1}; Val231, Leu223, Leu227, Gly409, Ala381; conventional hydrogen bond, unfavorable acceptor-acceptor, alkyl) (**Figs. 1–9**).

Moreover, compound **6** (–35.1456 kJ mol^{-1}; Val88, Leu363, Tyr79, Gln71, Ile75, Val85, Leu84, Tyr49; conventional hydrogen bond, pi-alkyl, alkyl); compound **7** (–33.0536 kJ mol^{-1}; Glu270, Ile426, Gly440, Asn423, Arg430; conventional hydrogen bond, unfavorable donor-donor, alkyl); compound **8** (–33.0536 kJ mol^{-1}; Lys442, Ser443, Cys439, Asp415, Asp441, Arg404, Pro221, Phe220, Met186, Arg222; conventional hydrogen bond, carbon hydrogen bond, pi-cation, pi-anion, pi-alkyl); compound **9** (-35.9824 kJ mol^{-1}; Arg152, Pro178, Phe148, Tyr180, Gly176, Arg349; conventional hydrogen bond, carbon hydrogen bond, pi-cation, pi-pi stacked, pi-stacked); compound **10** (–33.0536 kJ mol^{-1}; Leu355, Ile131, Pro344, Gln129, Leu130, Arg343; conventional hydrogen bond, carbon hydrogen bond, unfavorable donor-donor, unfavorable acceptor-acceptor, pi-sigma, alkyl).

According to the report shown in **Table 3**, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (compound **9**) proved to be superior based on the docking score of –35.9824 kJ mol^{-1} when compared to other studied compounds as well as the reference drug (clobazam). Oyeneyin *et al.* (2022) reported that lower binding affinity value of any molecule is an indication that such compound has a higher potential ability to inhibit than other studied compounds; thus, the selection of compound **9** as superior to other studied compound was considered appropriate. As shown in **Fig. 9**, series of nonbonding interactions were observed in the interaction between 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (compound **9**) and 4-aminobutyrate-aminotransferase; the nonbonding interaction involved wee conventional hydrogen bond, carbon hydrogen, pi-pi stacked and pi-alkyl. The conventional hydrogen bond was observed between Tyr180 and hydrogen (H14), Gly176 and hydrogen (H11) as well as Arg349 and oxygen (O7), which showed the specificity of compound **9** in the active site of 4-aminobutyrate-aminotransferase. Also, the hydrogen bond formed by compound **9** with the studied receptor was observed to enhance the exactness of calculated binding affinity (**Fig. 10**). Also, carbon hydrogen bond was observed between Pro178 and oxygen (O1); pi-cation interaction was observed between Arg349 and the aromatic ring attached to the parent compound; its presence between Arg349 and Pi-electron cloud in the aromatic compound was observed to enhance the lowest calculated binding affinity value when compared to the binding for other studied compounds as well as the binding score for the reference drug. The result also revealed the level of bioavailability, selectivity, steadiness, and lipophilicity of 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (compound **9**) to be more desirable when compares to that of the other studied compounds and clobazam (referenced drug).

The presence of pi-pi stacked (Phe148 and the electron cloud of the aromatic ring of the parent compound) and pi-alkyl (Pro178 and Arg152 attracted to the electron cloud of the aromatic ring of the studied compound) interactions also augmented the accomplishment of lowest binding score by compound **9** when compared to other studied compounds (**Fig. 11**).

Yan *et al.* (2022) investigated the activity of *A. spinulosa* leaves as potential anti-Alzheimer disease agents. It was observed that the polyphenols isolated from *A. spinulosa* leaves were excellent antioxidant agents and a potential ingredient for the alleviation of Alzheimer disease. Therefore, their report agreed well with the work carried out in this study as antiepilepsy agents. Also, the activity of *Alsophila* spp. against Gram positive and negative bacteria using the Kirby–Bauer disc diffusion method was investigated by Longtine and Tejedor (2017). It was observed that ethanolic extract of *Alsophila* spp. proved to be more active again Gram positive than Gram negative bacteria. The activity of these plants as anti-Gram positive bacteria goes in line with the *A. spinulosa* as antiepilepsy.

Table 3. Calculated binding score.

	Binding Affinity (kJ mol^{-1})	Residues involved in the interactions	Types of Nonbonding interaction involved
1	−33.472	Lys442, Asp441, Asp415, Arg404, Met186, Arg222	Conventional hydrogen bond, carbon hydrogen bond, pi-cation, pi-anion, pi-alkyl
2	−35.564	Cys169, Phe161, Arg156, Pro178, Arg152, Arg349, Tyr180,	Conventional hydrogen bond, pi-cation, pi-sulfur, pi-pi stacked, pi-alkyl
3	−34.7272	Lys145, Pro178, Trp215, Met149, Phe144, Phe148, Phe213, Cys177, Gly176	Carbon hydrogen bond, alkyl, pi-alkyl
4	−32.6352	Phe148, Arg349, Tyr180, Pro178, Arg156, Arg152, Gly176	Conventional hydrogen bond, unfavorable donor-donor, pi-pi stacked, pi-alkyl
5	−33.472	Val231, Leu223, Leu227, Gly409, Ala381	Conventional hydrogen bond, unfavorable acceptor-acceptor, alkyl
6	−35.1456	Val88, Leu363, Tyr79, Gln71, Ile75, Val85, Leu84, Tyr49	Conventional hydrogen bond, pi-alkyl, alkyl
7	−33.0536	Glu270, Ile426, Gly440, Asn423, Arg430	Conventional hydrogen bond, unfavorable donor-donor, alkyl
8	−33.0536	Lys442, Ser443, Cys439, Asp415, Asp441, Arg404, Pro221, Phe220, Met186, Arg222	Conventional hydrogen bond, carbon hydrogen bond, pi-cation, pi-anion, pi-alkyl
9	−35.9824	Arg152, Pro178, Phe148, Tyr180, Gly176, Arg349	Conventional hydrogen bond, carbon hydrogen bond, pi-cation, pi-pi stacked, pi-stacked
10	−33.0536	Leu355, Ile131, Pro344, Gln129, Leu130, Arg343	Conventional hydrogen bond, carbon hydrogen bond, unfavorable donor-donor, unfavorable acceptor-acceptor, pi-sigma, alkyl
Clobazam	−31.7984	-	-

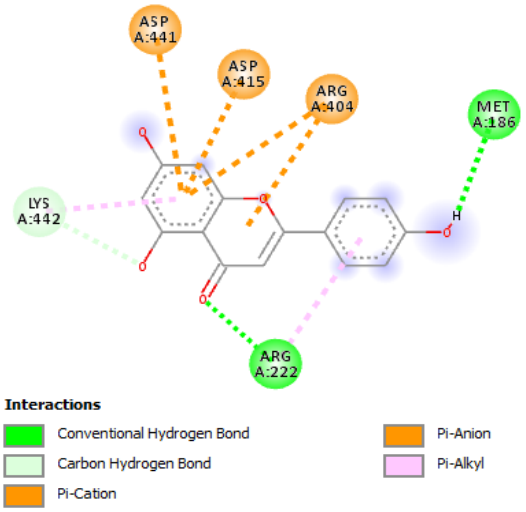


Figure 1. 2D structures of interaction between compound **1** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

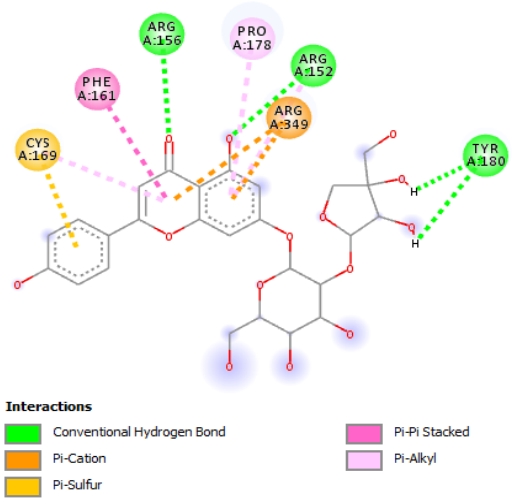


Figure 2. 2D structures of interaction between compound **2** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

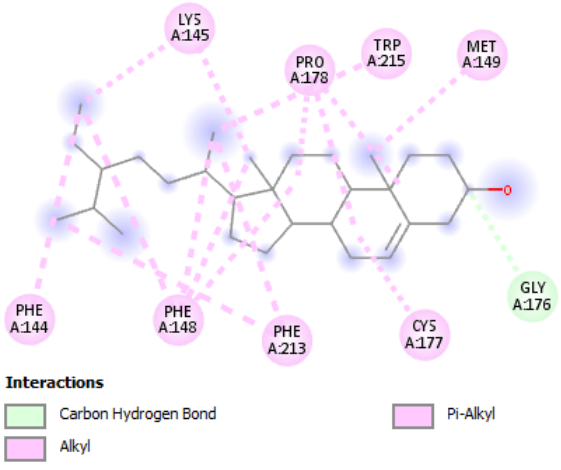


Figure 3. 2D structures of interaction between compound **3** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

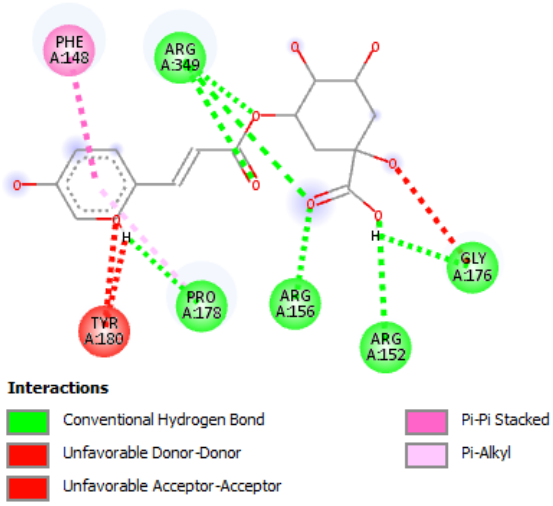


Figure 4. 2D structures of interaction between compound **4** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

https://doi.org/10.26850/1678-4618.eq.v49.2024.e1492

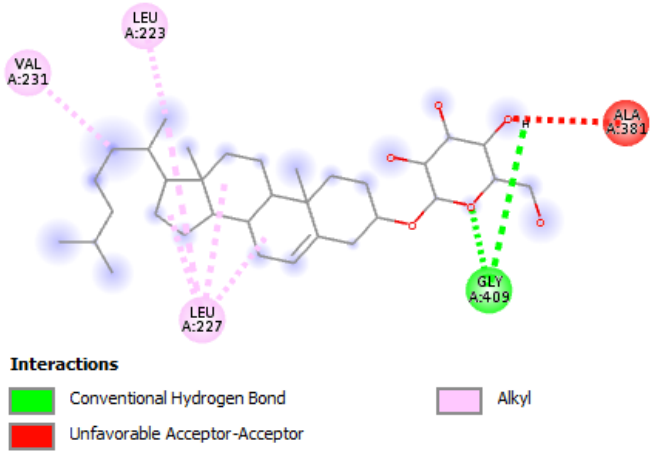


Figure 5. 2D structures of interaction between compound **5** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

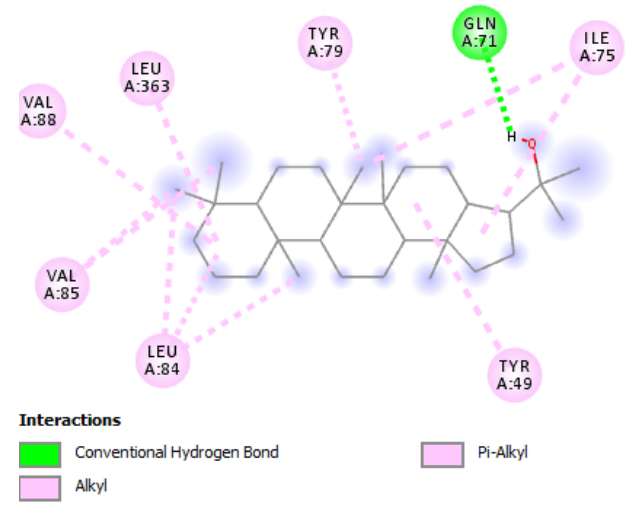


Figure 6. 2D structures of interaction between compound **6** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

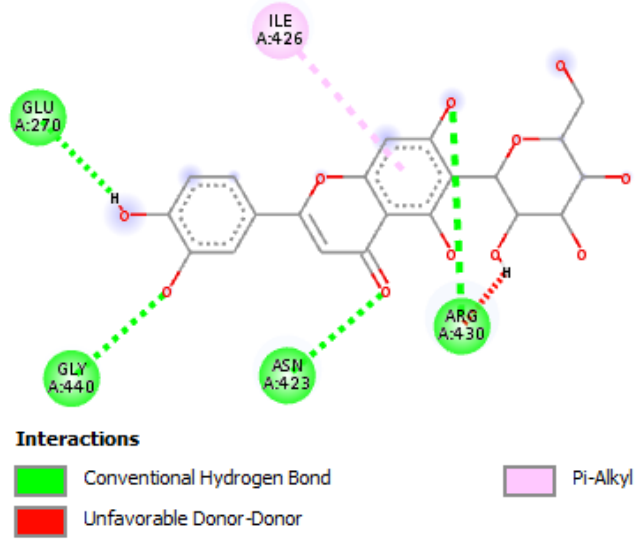


Figure 7. 2D structures of interaction between compound **7** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

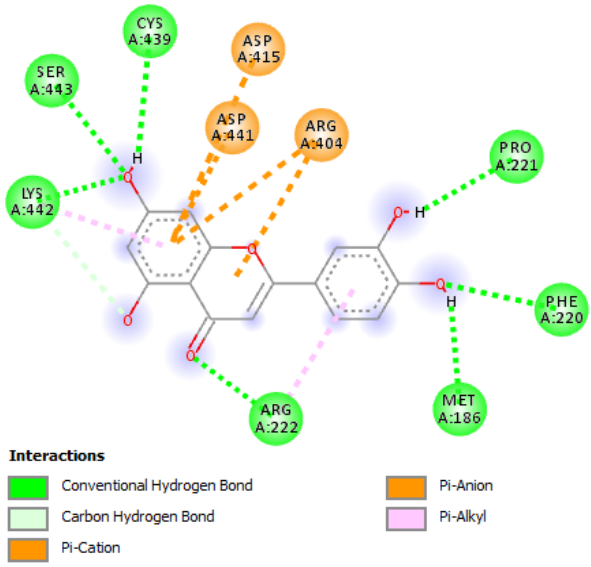


Figure 8. 2D structures of interaction between compound **8** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

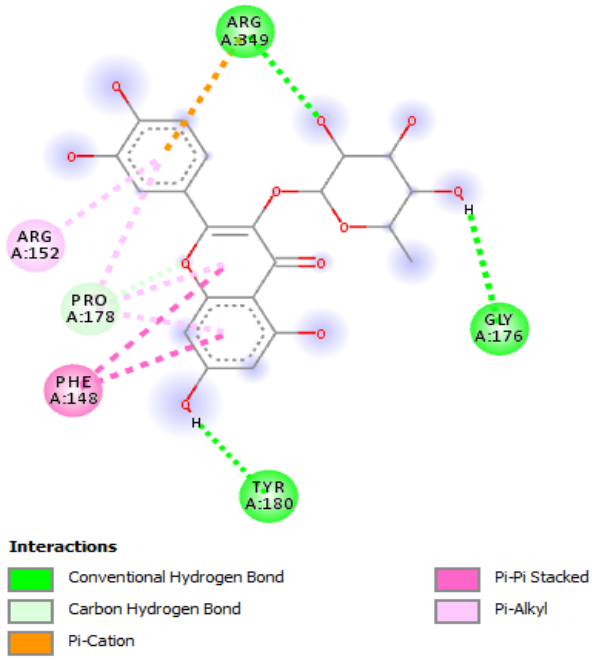


Figure 9. 2D structures of interaction between compound **9** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv)

https://doi.org/10.26850/1678-4618.eq.v49.2024.e1492

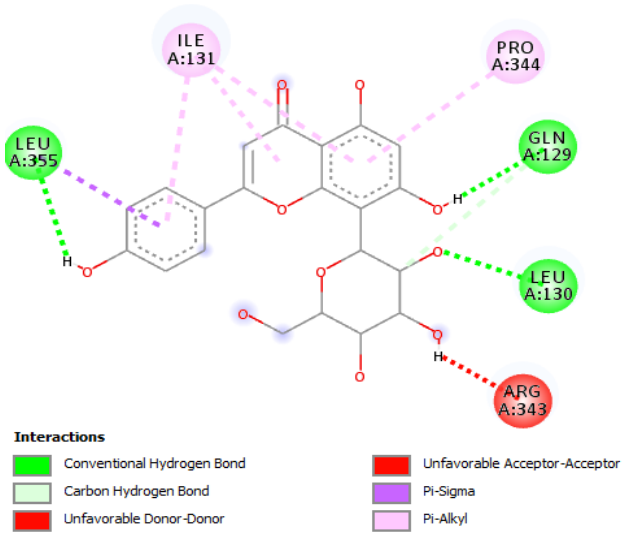


Figure 10. 2D structures of interaction between compound **10** and 4-aminobutyrate-aminotransferase (PDB ID: 1ohv).

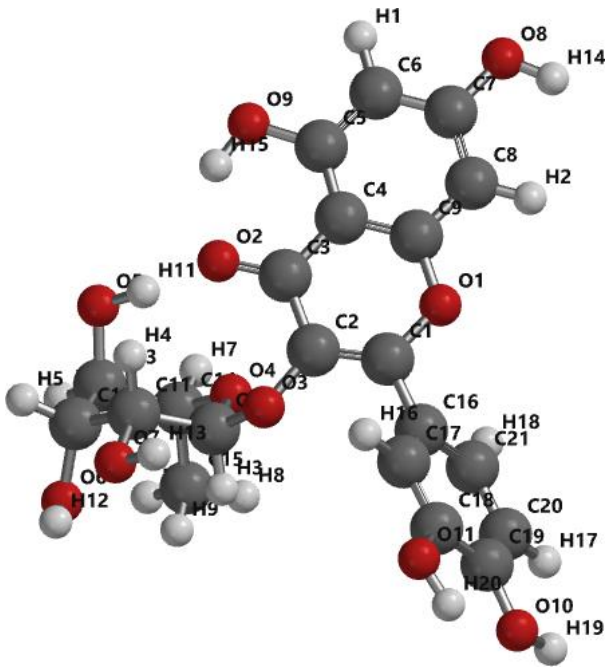


Figure 11. 3D structure of 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (compound **9**).

3.3. Pharmacokinetic analysis

The calculated ADMET features were obtained using ADMETsar (Cheng *et al.*, 2012). The ADMET properties compound with the lowest binding score (compound **9**) and the reference drug (clobazam) were investigated and the result for each compound are shown in **Tables 4** and **5**. The ADMET properties obtained for compound **9** were in a close range to the properties obtained for the reference drug. This indicates that 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (compound **9**) possess a greater attribute of a drug to inhibit 4-aminobutyrate-aminotransferase thereby downregulate epilepsy.

Table 4. Pharmacokinetic prediction for compound **9**.

ADMET Predicted Profile --- Classification		
Model	**Result**	**Probability**
Absorption		
Blood-brain barrier	BBB-	0.7568
Human intestinal absorption	HIA+	0.9051
Caco-2 permeability	Caco2-	0.7493
P-glycoprotein substrate	Substrate	0.6415
P-glycoprotein inhibitor	Noninhibitor Noninhibitor	0.8740 0.7784
Renal organic cation transporter	Noninhibitor	0.9396
Distribution		
Subcellular localization	Mitochondria	0.7163
Metabolism		
CYP450 2C9 substrate	Nonsubstrate	0.7557
CYP450 2D6 substrate	Nonsubstrate	0.9171
CYP450 3A4 substrate	Nonsubstrate	0.6312
CYP450 1A2 inhibitor	Noninhibitor	0.5306
CYP450 2C9 inhibitor	Noninhibitor	0.8538
CYP450 2D6 inhibitor	Noninhibitor	0.9547
CYP450 2C19 inhibitor	Noninhibitor	0.8339
CYP450 3A4 inhibitor	Noninhibitor	0.7109
CYP inhibitory promiscuity	Low CYP inhibitory promiscuity	0.5648
Human ether-a-go-go-related gene inhibition	Weak inhibitor Noninhibitor	0.9846 0.8181
AMES toxicity	Non-AMES toxic	0.9319
Carcinogens	Noncarcinogens	0.9461
Fish toxicity	High FHMT	0.9657
Tetrahymena pyriformis toxicity	High TPT	0.9945

Honey bee toxicity	High HBT	0.6560
Biodegradation	Not biodegradable	0.9073
Acute oral toxicity	III	0.5184
Carcinogenicity (three-class)	Nonrequired	0.6170
ADMET Predicted Profile --- Regression		
Model	**Value**	**Unit**
Absorption		
Aqueous solubility	−3.4974	LogS
Caco-2 permeability	−0.3114	LogPapp, cm s^{-1}
Rat acute toxicity	2.5458	LD50, mol kg^{-1}
Fish toxicity	0.6766	pLC50, mg L^{-1}
Tetrahymena pyriformis toxicity	0.8401	pIGC50, ug L^{-1}

Table 5. Pharmacokinetic prediction for Clobazam.

ADMET Predicted Profile --- Classification		
Model	**Result**	**Probability**
Absorption		
Blood-brain barrier	BBB+	0.9904
Human intestinal absorption	HIA+	0.9900
Caco-2 permeability	Caco2+	0.7487
P-glycoprotein substrate	Nonsubstrate	0.5733
P-glycoprotein inhibitor	Noninhibitor	0.5462
	Noninhibitor	0.9204
Renal organic cation transporter	Noninhibitor	0.7373
Distribution		
Subcellular localization	Mitochondria	0.4586
Metabolism		
CYP450 2C9 substrate	Nonsubstrate	0.7058
CYP450 2D6 substrate	Nonsubstrate	0.8607
CYP450 3A4 substrate	Substrate	0.6871
CYP450 1A2 inhibitor	Noninhibitor	0.6829
CYP450 2C9 inhibitor	Noninhibitor	0.5296
CYP450 2D6 inhibitor	Noninhibitor	0.8908
CYP450 2C19 inhibitor	Noninhibitor	0.5791
CYP450 3A4 inhibitor	Inhibitor	0.7008
CYP inhibitory promiscuity	Low CYP inhibitory promiscuity	0.5308
Excretion		
Toxicity		
Human ether-a-go-go-related gene inhibition	Weak inhibitor	0.9896
	Noninhibitor	0.8651
AMES toxicity	Non-AMES toxic	0.9132
Carcinogens	Noncarcinogens	0.7846
Fish toxicity	High FHMT	0.9713
Tetrahymena pyriformis toxicity	High TPT	0.9399
Honey bee toxicity	Low HBT	0.9163
Biodegradation	Not biodegradable	1.0000
Acute oral toxicity	IV	0.6201
Carcinogenicity (three-class)	Nonrequired	0.5725
ADMET Predicted Profile --- Regression		
Absorption		
Aqueous solubility	−4.5627	LogS
Caco-2 permeability	1.8526	LogPapp, cm s^{-1}
Rat acute toxicity	1.7313	LD50, mol kg^{-1}
Fish toxicity	1.0749	pLC50, mg L^{-1}
Tetrahymena pyriformis toxicity	0.8911	pIGC50, ug L^{-1}

4. Conclusions

Ten molecular compounds obtained from *A. spinulosa* leaves were investigated using *in silico* approach. The assessment of the potential inhibitory properties of selected phytochemicals present in *A. spinulosa* against human 4-aminobutyrate-aminotransferase and exploration of the potential nonbonding interaction involved in the studied complexes and their efficiency were accomplished in this work. The descriptors obtained from the optimized phytochemicals revealed that the studied medicinal plant have potential antiepileptic capacity. Moreover, the selected phytochemicals and the studied 4-aminobutyrate-aminotransferase (PDB ID: 1ohv), which were subjected to docking study, resulted into series of binding scores to expose the inhibiting capability of each compound. Compound **9** (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-

trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one) proved to possess highest binding strength to inhibit 4-aminobutyrate-aminotransferase than other selected phytochemicals in *A. spinulosa* leaves and the reference drug thereby down-regulating epilepsy. The pharmacokinetic features calculated for compound **9** and clobazam (reference drug) revealed that compound **9** (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one) have superior characteristic to inhibit 4-aminobutyrate-aminotransferase than other selected studied phytochemicals obtained from *A. spinulosa* leaves, thereby hindering the operation of epilepsy in human. These findings may open door for the design and development of library of efficient 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one-based drug-like compounds as potential antiepileptic agent.

Authors' contributions

Conceptualization: Oyebamiji, A. K.; **Data curation**: Olujinmi, F. E.; **Formal Analysis**: Akintelu, S. A.; **Funding acquisition**: Not applicable; **Investigation**: Adetuyi, B. O.; Ogunlana, O. O.; **Methodology**: Semire, B.; **Project administration**: Oyebamiji, A. K.; **Resources**: Babalola, J. O.; **Software**: Semire, B.; **Supervision**: O'Reilly, R. K.; **Validation**: Olawoye, B. M.; Aworinde, J. O.; **Visualization**: Oyebamiji, A. K.; **Writing – original draft**: Oyebamiji, A. K.; Semire, B.; **Writing – review & editing**: Oyebamiji, A. K.

Data availability statement

All data sets were generated or analyzed in the current study.

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