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Stevia-Derived Diterpenoids as Potential Dopamine D2 Receptor Antagonists for Insomnia and Schizophrenia Therapy: An *In Silico* Study

Sentot Joko Raharjo[*,1], Dewi Ratih Tirto Sari [2]
Ernanin Dyah Wijayanti [3] and Yanty Maryanty [4]

[1]Pharmacy and Food Analyst Department, Polytechnic of Health of Putra Indonesia Malang. Malang, Indonesia.
[2]Pharmacy Department, Ibrahimy University, Situbondo, Indonesia.
[3]Pharmacy Department, Polytechnic of Health of Putra Indonesia Malang. Malang, Indonesia.
[4]Chemical Engineering, State Polytechnic of Malang, Malang, Indonesia.
***Corresponding author**
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Abstract

Insomnia is the second most common mental disorder and causes several health risks. Stevia water extract is a popular natural sweetener and promotes health benefits including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, anti-hypertension. This study investigates the potential of Diterpenoid-Water-Extract Compounds as a target for insomnia therapy through the use of dopamine receptors (D2/D4) *in silico*. This research method includes: Stevia water extract compounds resulting from LCMS analysis as ligands and proteins of D4 dopamine receptor (id: 5wiv) and D2 dopamine receptor (id: 6cm4) were taken from the database, then native ligands and bioactive compounds were docked again and their interactions were analyzed. The best binding affinity results are based on the stability of the interaction using molecular dynamics simulations. The docking results showed that several water stevia extract compounds bound to the same dopamine D2 and D4 receptor sites as the original ligand. Binding affinity shows relatively similar scores for both water and original stevia extract compounds against the D2-dopamine receptor. This result, molecular docking analysis of water stevia extract compounds shows that the active site interactions and binding affinity are the best for selective D2 dopamine receptors, including Steviolmonoside, Steviolbioside, Sterebin-G, -E, -B, -M, -A, and -K , Steviol, and Isosteviol. These diterpenoid compounds also have stable interactions with D2 dopamine in dynamic molecular simulations. The conclusion of this research is the diterpenoids compounds in water stevia extracts, such as Steviolbioside, Steviolmonoside, Rebaudioside G, Sterebin G, Sterebin M, Steviol, and Isosteviol have the ability to target insomnia therapy through D2 dopamine receptor inhibition/antagonist.
Keywords: Water-stevia-extracts, Diterpenoid compounds, D2-dopamin, Anti-insomnia

Introduction

Insomnia and schizophrenia have a complex and mutually exacerbating relationship through several biological and psychological mechanisms [(1,2)]. The key mechanism that links schizophrenia and insomnia biologically is the dopamine Dysfunction mechanism [(3-5)]. Dopamine dysfunction causes dopamine hyperactivity in schizophrenia and also disrupts sleep regulation through decreased melatonin and circadian rhythm disturbances, thus creating a close relationship between schizophrenia and insomnia [(6)]. Treatment that balances dopamine activity is important to address both of these conditions simultaneously[(7)]. In the management of schizophrenia and insomnia, dopamine mechanisms, namely the D2 dopamine (antagonist) and D4 dopamine (agonist) mechanisms, are complementary[(8,9)]. D2 dopamine (antagonist) plays\a role in reducing psychotic symptoms and providing a sedative effect, while D4 dopamine (agonist) helps balance dopamine activity to support a healthy sleep cycle and reduce insomnia [(10)]. This approach is important to improve the quality of life of schizophrenia patients who often experience sleep disorders [(11)].

Selectivity in the development of drug candidates is a key factor in the improvement of therapeutic efficacy and the minimization of side effects[(12)]. Selectivity in drug compound discovery is essential to ensure that the compound specifically targets certain molecules in the body.

Molecular in various neurobiological functions and psychopathological disorders, including schizophrenia[(14)]. Schizophrenia is a neurodevelopmental condition with a lifetime

prevalence estimate of 0.6% that includes symptoms from the positive, negative, and cognitive domains[15]. This condition is commonly characterized by anhedonia, loss of focus, disorganized speech, hallucinations, and irregular sleep patterns[16]. A major feature of many schizophrenia models is dysfunction in the connections from the midbrain to the striatum[17]. Schizophrenia often requires long-term therapy with antipsychotic drugs that target dopamine receptors[18]. Dopamine, a neuromodulator in the CNS, plays a crucial role in movement control, reward and reinforcement, and affective processes, making it a key factor in many psychiatric illnesses [19]. The actions of dopamine are mediated by a group of five G-protein coupled receptors (GPCRs) (D1, D2, D3, D4, and D5). The D2 dopamine receptor (DRD2) is the primary target for both typical and atypical antipsychotics [20]. Dopamine receptor agonists and antagonists have been employed for relieving symptoms of neuropsychiatric disorders [21]. Antagonizing D2 receptor activation has been identified as an effective treatment for lowering positive sensations. However, many of today's synthetic drugs cause significant side effects, such as motor impairment and cognitive dysfunction[22].

Stevia (*Stevia rebaudiana*) is a plant whose leaves can be used as a natural, low-calorie sweetener. Stevia has many biological activities, including antioxidant[23], anti-inflammatory[24], anti-diabetic[25], anti-cancer[26], and anti-hypertensive[27]. Stevia has been used for food and medicinal purposes for hundreds of years. The plant was first described in 1899 by Swiss botanist Moisés Santiago Bertoni. In 1931, two French chemists isolated the glycosides that give stevia its sweet taste. Stevia is extracted from the leaves of the *Stevia rebaudiana* plant, a South American shrub. The leaves contain steviol glycosides, which are chemicals that give stevia its sweet taste. Stevia is a non-nutritive sweetener that's 200–400 times sweeter than table sugar. Stevia extract, made the leaves are steeped in hot water to extract the sweet compounds. The extract is then separated, filtered, and purified. Stevia leaves contain many phytochemicals, including Stevioside, Rebaudioside A, and Flavonoids. Stevioside found in the leaves of Stevia rebaudiana Bertoni, Stevioside is 300 times sweeter than sucrose. Rebaudioside A is a sweetening compound that is 250 to 400 times sweeter than sucrose [28]. Flavonoids in stevia include flavones, flavonols, and flavanols. Stevia is a natural, non-caloric sweetener that is considered a safe and cost-effective alternative to artificial sweeteners. However, the safety profile and long-term effects of stevia use are still being studied. Some common methods, extraction methods use water solvents to extract steviol glycosides from stevia leaves by steeping, clarification, purification, alcohol rinsing, and alcohol removal, decolorization, and filtration[29]. Hexane solvent has been used to extract stevia from the leaves of the stevia plant for a variety of purposes, including antifungal activity, antibacterial activity and fractionation. Hexane extracts of stevia leaves have been shown to inhibit the growth of the fungus *Fusarium oxysporum*, which can cause significant losses in tomato cultivation[30]. Hexane extracts of stevia leaves also have been shown to have antibacterial activity against cariogenic bacteria[31]. Hexane has been used to fractionate methanol extracts of stevia leaves to isolate phenolic compounds and flavonoids[32].

Diterpenoid compounds, which are one of the groups found in water extracts of stevia, have been identified as low-calorie natural sweeteners and possess various biological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, antihypertensive, and others. Several diterpenoid compounds, such as steviolmonoside, steviolbioside, sterebin-G, sterebin-E, sterebin-B, sterebin-M, sterebin-A, sterebin-K, steviol, and isosteviol, are known to exhibit multiple biological activities. However, the potential of diterpenoid compounds as dopamine receptor inhibitors, and their specific benefits for the treatment mechanisms of schizophrenia and insomnia, have not been widely studied. The effectiveness of therapies for schizophrenia and insomnia is often limited by the side effects of existing synthetic drugs. Therefore, this study investigates diterpenoid compounds using an *in silico* analysis approach, including molecular docking and molecular dynamics, to determine their selectivity toward dopamine receptors (D2 and D4 subtypes). The urgency of this research lies in identifying potential dopamine inhibitor candidates, which will subsequently be confirmed and analysed through in vitro and in vivo studies, with the expectation that they will exhibit improved side effect profiles. Natural compounds in stevia may offer a safer alternative with significant therapeutic potential. This study aims to explore the dopamine receptor inhibitory activity of diterpenoid compounds in water stevia extracts and assess their potential application in the treatment of schizophrenia. Through an in-depth selectivity approach, it is expected to provide new insights into the mechanism of action of these diterpenoid compounds and their contribution as safer and more effective therapeutic candidates. The results of this study are anticipated to make a significant contribution to the development of new therapies that reduce the side effects commonly associated with synthetic drugs used for schizophrenia and

insomnia.

Materials and Methods

Stevia Material, Extraction and LC-MS analysis

Stevia rebaudiana Bertoni is cultivated in Ploso Village, Mojo Subdistrict, Kediri Regency, East Java, Indonesia. This plant was authentication in the Herbal Materia Medica Laboratory in Batu, East Java, Indonesia. Stevia simplicia weighing 25 grams was placed in a glass beaker, and then 250 mL of water solvent was added and stirred. The solvents were used separately. Maceration was carried out for 3 hours at room temperature, followed by sonication (200 W, 40 KHz) for 30 minutes at 70℃. The resulting extract was filtered, and the residue was macerated again with each solvent. The macerated filtrate was combined with the initial filtrate and then concentrated to a thickness of 50 mL using a rotary evaporator under vacuum at 55℃. Next, the extract was centrifuged for 10 minutes to remove any solids that might have escaped filtration. The resulting 40-50 mL filtrate was stored in the freezer until frozen, then the freezer drying process was carried out for 62 hours until the dry extract [33].

Quantitative and qualitative analysis of stevia water extract compounds with LC–MS/MS Shimadzu LCMS 8040.

The Shimadzu LCMS 8040 LC/MS was used to conduct high-resolution MS/MS analysis[34]. The chemical profile by liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis[35]. Sample preparation was carried out by weighing 1 mg of dry stevia extract, poured into 20 mL of distilled water in a 25 mL volumetric flask, dissolved and added distilled water to the mark. Quantitative and qualitative analysis of stevia sample with LC–MS/MS instruments was based on a triple mass spectrometer model Shimadzu LCMS 8040. Liquid chromatography with a gradient pump model LC-30 AD, degasser model DGU20A3R, column oven model CTO-10Asvp, and automatic model equipment auto sampler from Shimadzu (SIL) was performed. The column was separated by chromatography on Shimadzu Shim Pack FC-ODS (2 mm x 150 mm, 3 µm), injection volume 1 µL, capillary voltage 3.0 kV, column temperature 350°C, mobile phase mode isocratic, flow rate 0.5 mL/min, sampling cone 23.0 V, eluent methanol 90%, MS focused ion mode Io type $[M]^+$, collision energy 5.0 V, desolvation gas flow 60 mL/hr, desolvation temperature 350°C, fragmentation method, low energy CID Ionization, ESI Scanning 0.6 sec/scan (mz: 10-1000), source temperature 100°C, and run time 60 minutes.

In silico analysis

Molecular docking and dynamic analysis of the human D4 dopamine receptor and the D2 dopamine inhibitor

Protein Target

The structures of the human D4 dopamine receptor and the human D2 dopamine receptor were obtained from The Research Collaboratory for Structural Bioinformatics Protein Data Bank (https://www.rcsb.org), identified by PDB IDs 5wiv and 6cm4, respectively. The three-dimensional structures were optimized to evaluate the physicochemical properties of both the test ligands and native ligands using Gaussian software. This structural optimization was performed using the Density Functional Theory (DFT) computational method.

Molecular docking validation

Molecular docking validation was conducted by re-docking the native ligands nemonapride (CID156333) for the human D4 dopamine receptor (5wiv) and risperidone (CID5073) for the human D2 dopamine receptor (6cm4)—after removing their native ligands, using AutoDock 4.2 software. The docking validation was considered successful if the root-mean-square deviation (RMSD) value was less than 2 Å[36]. The molecular docking process was carried out using AutoDock Tools and AutoDock Vina.

Docking AutoDock Vina

Thirty-three diterpenoid compounds identified from LC-MS analysis of stevia dry extracts were selected as ligands were retrieved their structure from PubChem NCBI database. Ligand preparation was performed using LigParGen, a web-based service that generates force field parameters for organic molecules[37-39]. Both proteins and ligands were converted to the PDBQT format using AutoDock Tools 4.2. The optimized protein structures and ligands were saved in the same folder for docking.

For receptor preparation in AutoDock Tools, the application was launched, and the receptor was loaded using the "Read Molecule" option. Hydrogens were added by selecting "All Hydrogens," setting the method to "No Bond Order," and enabling atomic renumbering to account for the new hydrogens. The receptor was then saved in PDBQT format.

Ligand preparation involved opening the ligand file via "New Input." Once the ligand appeared in the workspace, the torsion tree was adjusted to define the number of rotatable bonds, and the ligand was saved in PDBQT format.

To define the docking binding site, the receptor (in PDBQT format) was selected, and the grid box was set through the grid menu by adjusting the coordinates along the x (red), y (green), and z (blue) axes. Discovery Studio Visualizer was used to identify the active or binding site on the receptor by right-clicking and searching for the target area.

The coordinates (x, y, z) obtained from Discovery Studio were then entered into AutoDock Tools to accurately position the grid box[40]. Finally, the optimized compounds were re-docked with the proteins from which native ligands had been removed, using AutoDock 4.2 and the defined grid box. The docking results provided binding affinity values and inhibition constants for the compounds with the lowest binding energy and most favorable conformations to the target proteins[36].

Molecular docking visualization

Docking simulations were performed between thirty-three diterpenoid compounds identified from LC-MS analysis of stevia dry extracts and the human D2 dopamine receptor (PDB ID: 6cm4) as well as the human D4 dopamine receptor (PDB ID: 5wiv) using AutoDock Vina 4.2 software. Following the preparation of both receptors and ligands, the docking procedure was initiated via the command prompt. The resulting docked complexes were visualized using Discovery Studio 4.1 software[40]. The analysis focused on identifying the ligand conformations exhibiting the highest binding affinity, determined by the most negative binding energy values, and examining the binding interactions with amino acid residues in both 2D and 3D representations. These binding affinity values were compared against those of the native ligands to assess relative binding strengths.

Molecular dynamic of ligand steviolmonoside, steviolbioside, sterebin-G, sterebin-E, sterebin-B, sterebin-M, sterebin-A, and sterebin-K, steviol, and isosteviol in the protein 6cm4_D2-dopamin

Molecular dynamics (MD) simulations were conducted to investigate the binding interactions of several ligand compounds of steviolmonoside, steviolbioside, sterebin-G, sterebin-E, sterebin-B, sterebin-M, sterebin-A, and sterebin-K, steviol, and isosteviol with the 6cm4_D2 dopamine receptor, focusing on those ligands that exhibited the best docking scores. The simulations were performed using OpenMM on the Google Collab platform.

Ligand preparation.

The three-dimensional structures of the ligands were retrieved from the PubChem Open Chemistry Database. The SMILES format structures of the compounds were converted into *.pdb files using LigParGen, a web-based tool that generates force field (FF) parameters for organic molecules and ligands[32-34].

Simulation Environment Setup.

To perform the MD simulations, necessary software libraries and packages were installed, including Anaconda, OpenMM, PyTraj, py3Dmol, ProLIF, Numpy, Matplotlib, and AmberTools. The ligand and protein *.pdb files were uploaded and managed on Google Drive and Google Colab.

MD Simulation Protocol

The simulations followed the protocol outlined by Pablo R. Arantes *et al*.[41], with parameters set to generate the protein topology using the FF19SB force field and TIP3P water model. The system was neutralized with NaCl ions at a concentration of 0.15 M using AMBER tleap. Ligand topology was generated using the GAFF2 force field.

The equilibration protocol included 1,000 minimization steps, a 5-nanosecond simulation time, and an integration time step of 2 femtoseconds. The system was maintained at a temperature of 310ºK and a pressure of 1 bar. Trajectory and log files were recorded every 10 picoseconds.

The production MD simulation was run for 10 nanoseconds with similar parameters: an integration time step of 2 femtoseconds, temperature of 310°K, pressure of 1 bar, and data recording frequencies of 10 picoseconds for both trajectory and log files.

Binding Energy Calculations and Analysis

Interaction energies and solvation free energies were calculated for the ligand-receptor complexes, receptors, and ligands. The binding free energy was estimated by averaging these values. Both MM-GBSA and MM-PBSA methods were employed for binding energy calculations to provide comparative results. The GB/SA input parameters included the OBC model (igb=2) and a salt concentration of 0.15 M.

Additional analyses included generating LigPlot diagrams before and after simulation, calculating interaction energies, measuring distances between the ligand and catalytic site residues as well as specific amino acid residues, computing the root mean square deviation (RMSD) of the protein's Cα atoms, plotting RMSD distributions, interaction energy average, among and other assessments[41].

Results and Discussion

Water stevia extraction and Dry stevia extract LC-MS analyzed

The LC-MS profile identified a total of 126 active compounds, as illustrated in Figure 1 [a]. The composition of secondary metabolite groups revealed that the compounds consist of approximately 45% flavonoids and flavonoid glycosides, 34% diterpenoids and diterpenoid glycosides, 10% sesquiterpenoids, 6% simple phenols, 2% triterpenoids, and 10% other compounds, as shown in Figure 1 [B]. These predominantly polar compounds are present in the water extracts of stevia[42,43]. Among the

diterpenoid glycosides, most belong to the ent-kaurane and labdane types. Ent-kaurane glycosides are the primary constituents of stevia leaves, with stevioside being the most abundant and commercially significant glycoside within this group[44]. During the extraction of stevia leaves using water as the solvent, several compounds were identified through LC-MS analysis. These included diterpenoids such as steviol glycoside rebaudioside (34%), tetracyclic diterpenoids (19%), stevioside diterpenoids (11%), diterpenoid glucosides (8%), and other diterpenoids (6%). The diterpenoid group and diterpenoid glycosides constitute approximately 34% of the secondary metabolites present in the water stevia extract. Similar studies have reported that commercial extracts from *Stevia rebaudiana* leaves contain not only the well-known steviol glycosides like rebaudiosides A-F, rubusoside, and dulcoside A, but also a newly isolated diterpene glycoside[45,46]. In this study, the LC-MS profile of dry stevia extract obtained from simplicia extraction using water as the solvent identified a total of 33 diterpenoid compounds, as presented in Figure 1C and Table 1. The compounds were reported along with their retention times, percentage compositions, and diterpenoid subclassifications. The predominant compounds included stevioside (3.74%), rebaudioside B (2.29%), steviolbioside (1.75%), rubusoside (1.60%), steviolmonoside (1.56%), dulcoside A (1.90%), rebaudioside A (1.73%), rebaudioside C (1.55%), among others. Stevioside, a natural sweetener derived from the leaves of the *Stevia rebaudiana* plant, is a white, odorless, crystalline substance that is over 300 times sweeter than sucrose. It contains no calories, remains stable in solid form, is resistant to decomposition in acidic beverages at 22°C, and does not break down when exposed to heat[47,48]. Stevioside has many health benefits, some include a source of vitamins, minerals, antioxidants, and antimicrobials, helps lower high blood pressure, helps improve the nutritional status of diabetes sufferers[49,50]. Rebaudioside B is a non-caloric sweetener found in stevia leaves. It has a variety of activities, including sweetening[50], antioxidant[51], anti-inflammatory properties, liver protection, and lipid metabolism[52]. Steviol glycosides also may have antitumor, antiviral, antimicrobial, antihypertensive, and antifungal activities[53]. Steviolbioside is a sweetener and metabolite of stevioside and rebaudioside A, which are found in the leaves of the *Stevia rebaudiana* plant[54]. Steviolbioside has many activities, including anti-cancer[55], anti-tuberculosis[56], food additive[54], and intermediate in medications[57]. Steviolbioside is also a rare sweetener that is about 200 to 400 times sweeter than table sugar. It is a non-nutritive sweetener, meaning it has no calories, carbohydrates, or artificial ingredient[58]. Stevia diterpenoid compounds as sweetener components have many pharmacological activities, such as anti-diabetic, anti-inflammatory, anti-cancer, and cardio-vascular protective properties[59]. To date, no research has explored the role of this group of compounds in the mechanisms underlying schizophrenia and insomnia. However, the potential therapeutic effects of these candidate compounds in treating schizophrenia and insomnia, which have not yet been studied, can be predicted through *in silico* analysis[60].

In silico analysis

The negative effects of current synthetic medications often hinder the efficacy of schizophrenia therapy. This *in silico* molecular docking study aims to identify drugs with a high selectivity profile for dopamine receptors[16]. The natural ingredients of diterpenoid compounds from water stevia extracts can be expected to be a much safer substitute with various possible medical uses. The initial stage of molecular docking analysis validates native ligands in human D2 dopamine (id: 6cm4) and human D4 dopamine (id: 5mwi). The native ligand of D2 dopamine is nemonapride (CID156333) and the native ligand of D4 dopamine is risperidone (CID5073). The native ligands (nemonapride (CID156333) from D2 dopamine (id: 6cm4) and risperidone (CID5073) from D4 dopamine (id: 5mwi)) were re-docked at the predetermined grid box coordinate center. This process aims to validate and optimize the correct positioning of the binding site in the docking method, where the resulting pose will be compared with the original pose of the native ligand structure to see whether it has similar interactions[61]. The success parameters of this application are based on overlapping poses and the calculation of an RMSD (Root Mean Square Deviation) value of ≤ 2 Å, which states the distance between the conformational deviations of the ligand pose that has gone through the docking stage with the actual ligand[62].

In this study, the native ligands nemonapride (CID156333) from the D4 dopamine receptor (PDB ID: 5wiv) and risperidone (CID5073) from the D2 dopamine receptor (PDB ID: 6cm4) were re-docked at the predefined grid box center. The re-docking results showed poses closely matching the original ligand conformations, with RMSD values of ≤ 2 Å. This confirms the validity of the AutoDock Vina docking protocol, demonstrating its ability to accurately predict ligand-target interactions and justifying the use of these grid box coordinates for docking test compounds[63].

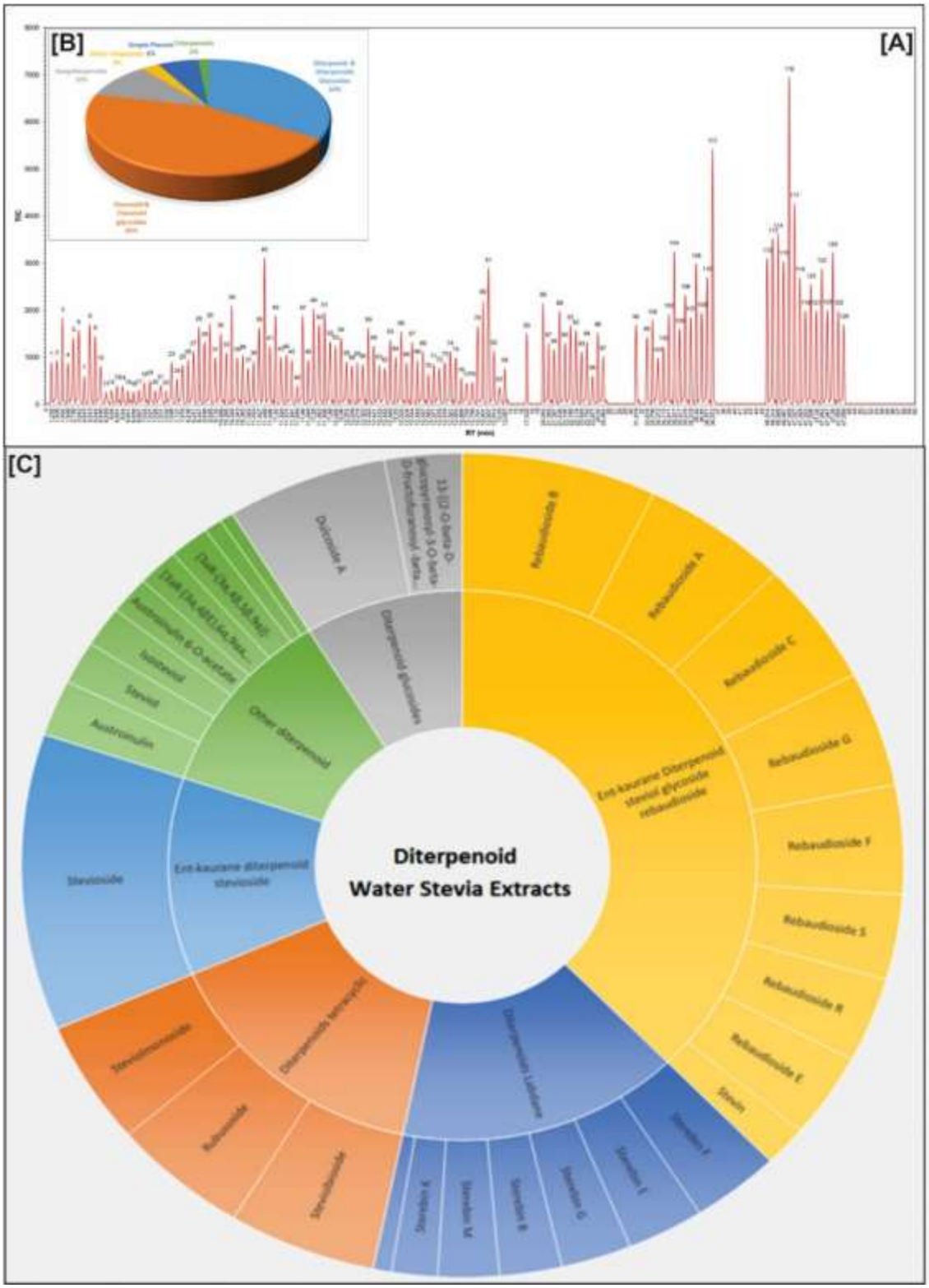


Figure 1. [A] TIC of LCMS Diterpenoid-Stevia Compounds Extract with Water Extract using LCMS Shimadzu LCMS–8040 LC/MS Column Shimadzu Shim Pack FC-ODS (2 mm x 150 mm, 3 µm), eluen methanol 90%; [B] Metabolic secondary composition in water stevia extracts by maceration-sonfication; [C] Compounds of Diterpenoid Stevia Water Extracts

Table 1. Bioactive Diterpenoid compounds from water stevia extracts by LCMS analysis

No.	t_R	Bioactive Diterpenoid compounds from LCMS analysis	% relative	Sub Diterpenoids Classification
1	116	Stevioside (CID442089)	3.74839	Diterpenoid stevioside
2	117	Rebaudioside B (CID21593623)	2.29978	Diterpenoid steviol glycoside
3	105	Steviolbioside (CID16401639)	1.75034	Diterpenoids tetracyclic
4	108	Rubusoside (CID24721373)	1.60963	Diterpenoids tetracyclic
5	81	Steviolmonoside (CID21593622)	1.56115	Diterpenoids tetracyclic
6	113	Dulcoside A (CID72941582)	1.90136	Diterpenoid glycoside
7	124	Rebaudioside A (CID6918840)	1.73896	Diterpenoid steviol glycoside
8	122	Rebaudioside C (CID60208888)	1.55493	Diterpenoid steviol glycoside
9	118	Rebaudioside G (CID21591681)	1.45328	Diterpenoid steviol glycoside
10	120	Rebaudioside F (CID72941817)	1.37726	Diterpenoid steviol glycoside
11	49	Sterebin I (CID101263051)	1.09796	Diterpenoids Labdane
12	123	Rebaudioside S (CID132566506)	1.07750	Diterpenoid steviol glycoside
13	121	Rebaudioside R (CID132566505)	1.07217	Diterpenoid steviol glycoside
14	125	Rebaudioside E (CID72710721)	1.07093	Diterpenoid steviol glycoside
15	51	Sterebin F (CID13996076)	1.04890	Diterpenoids Labdane
16	50	Sterebin E (CID13996075)	0.90874	Diterpenoids Labdane
17	126	13-[(2-O-beta-D-gluco pyranosyl-3-O-beta-D-fructofura nosyl -beta-D-glucopyranosyl) oxy]kaur-16-en-18-oic acid beta-D-glucopyranosyl ester (CID101623749)	0.91591	Diterpenoid glucosides
18	48	Sterebin G (CID13996077)	0.83371	Diterpenoids Labdane
19	65	Sterebin B (CID71694414)	0.73800	Diterpenoids Labdane
20	52	Sterebin M (CID21589507)	0.72054	Diterpenoids Labdane
21	64	[3aR[3α,4α(R*),6α,9α,9β]]2,3,3a,4,5,6,6a,7,9, 9b deca hydro-9-methyl-3,6-bis (methylene)-2-oxoazu leno[4,5-b] furan-4-yl- ester-2,5-dihydro-5-hydroxy-3-furan carboxylic acid (CID162934623)	0.71304	Diterpenoids
22	27	Sterebin A (CID21681091)	0,60689	Diterpenoids Labdane
23	77	Sterebin K (CID21589505)	0.54291	Diterpenoids Labdane
24	43	Steviol (CID452967)	0.54218	Diterpenoids Kaurane
25	45	Isosteviol (CID99514)	0.51050	Diterpenoids Kaurane
26	26	Rebaudioside O (CID92023639)	0.51038	Diterpenoid steviol glycoside
27	73	Austroinulin 6-O-acetate (CID131752054)	0.48324	Diterpenoids Labdane
28	57	[3aR-[3α,4βE),6α,9αa, 9β]]2,3,3a,4,5,6,6a,7,9a,9b deca hydro-9-methyl-3,6bis (methylene)-2-oxoazu leno [4,5-b] furan-4-yl ester-4-hydroxy-2-methyl 2-butenoic acid (CID13994647)	0.48221	Diterpenoids
29	24	Sterebin D (CID14396288)	0.29363	Diterpenoids Labdane
30	46	Austroinulin (CID11472742)	0.21559	Diterpenoids Labdane
31	14	[3R-(3α,3α,4α,9α)]-3a,4,4a,7,9,9a-hexahydro-3,5,8- trimethylazuleno [6,5b]furan-2(3H)-one (CID162900224)	0.21331	Diterpenoids
32	15	[3aR-(3α,4β,5β,9α)]-3a,4,4a,5,6,7,8,9a-Octahydro4a,5-dimethyl-3-methylenenaphtho [2,3-b]furan-2(3H)-one (CID91704079)	0.16074	Diterpenoids
33	66	[3aR-[3α,4β(R*),9α, 9β]]-2,5dihydro-5-hydroxy-2,3,3a,4,5,7, 9a,9b-octahydro-6,9-dimethyl-3-methylene-2-oxoazuleno[4,5-b]furan-4-yl ester 3-furan carboxylic acid (CID162977543)	0.47803	Diterpenoids

The re-docking results showed poses closely matching the original ligand conformations, with RMSD values of ≤ 2 Å. This confirms the validity of the AutoDock Vina docking protocol, demonstrating its ability to accurately predict ligand-target interactions and justifying the use of these grid box coordinates for docking test compounds [63]. As illustrated in Figure 2, the overlap between the original and re-docked ligand poses indicates similar interactions and no significant positional differences. These findings align with previous studies, and notably, the RMSD value obtained here is even lower (closer to zero), suggesting improved structural conformation accuracy compared to earlier reports[64]. The greater the RMSD value obtained indicates the greater the distance between the pose of the docking ligand and the original ligand [65].

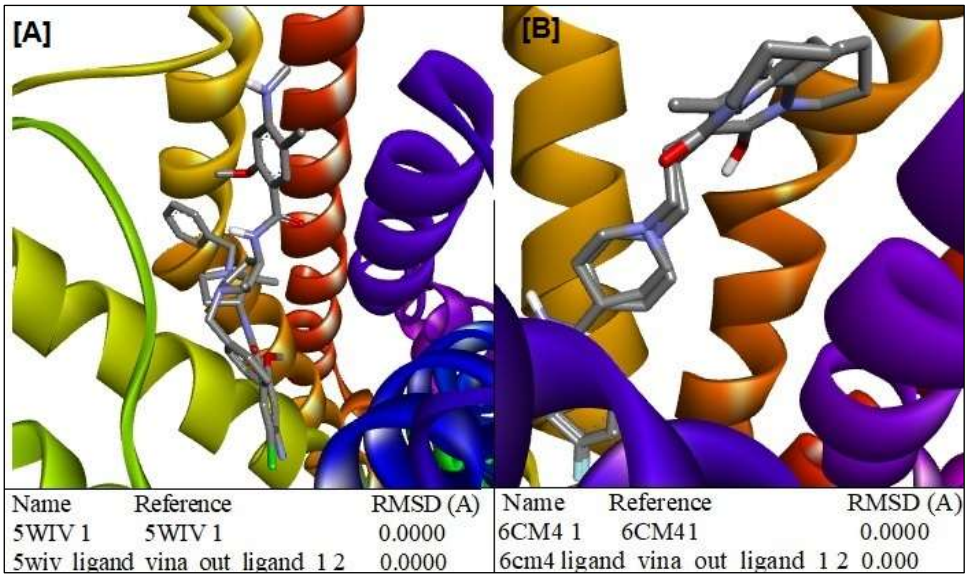


Figure 2. Visualization comparing the native ligands: [A] Risperidone (CID5073) bound to the D4 dopamine receptor (PDB ID: 5wiv) and, [B] Nemonapride (CID156333) bound to the D2 dopamine receptor (PDB ID: 6cm4), along with the positions of the re-docked ligand results.

The test ligands used are nemonapride, risperidone as native and steviolbioside as bioactive, downloaded in 3D structure form via the Pubchem website. Next, the structure of the test ligand is subjected to geometric optimization using LigParGen is a web-based service that provides force field (FF) parameters for organic molecules or ligands[39,66]. Then the polar H-atoms and partial charges of the gasteiger atoms are added. The addition of polar H-atoms and charges in the atomic coordinate model aims to optimize predictions of ligand binding models and increase the accuracy of interactions between ligands and target proteins, as well as helping to reduce the possibility of errors in interaction energy calculations. In AutoDock Vina docking, a coordinate model is used, where the exact position of atoms and their charges are important parameters in determining interactions, where in general the interactions that occur between ligands and macromolecules are hydrogen bonds, while generally crystallographic structures lack H-atoms, so polar H-atoms need to be added [59]. The geometric optimization process aims to position the atoms in the most ideal geometric structure arrangement and obtain the most stable compound structure[60]. The result of docking is to obtain binding affinity values originating from bond interactions formed from the conformation of the ligand with the target protein human D2-dopamine (6cm4) and human D4-dopamine receptor (5wiv). This research uses AutoDock Vina to analyze interactions between sequential ligands and receptors from the most stable conformation. Nemonapride (CID156333) is a commercial drug known to act as a human D4 dopamine receptor agonist inhibitor, while resperidone (CID5073) act as a human D2 dopamine receptor antagonist. Figure 3 shows the 2D and 3D interactions of the human D2 dopamine receptor (PDB ID: 6cm4) with risperidone, and the human D4 dopamine receptor (PDB ID: 5wiv) with Nemonapride. Figure 4 illustrates the 2D and 3D interactions of the human D2 dopamine receptor (PDB ID: 6cm4) with steviolbioside (CID16401639), as well as the human D4 dopamine receptor (PDB ID: 5wiv) with Steviolbioside (CID16401639).Therefore, in this study on the selectivity of diterpenoid compounds from *Stevia rebaudiana*, the binding affinity values of the test ligands to the D2 and D4 dopamine receptors were compared with those of nemonapride for the D4 dopamine receptor and risperidone for the D2 dopamine receptor, as shown in Figure 3.

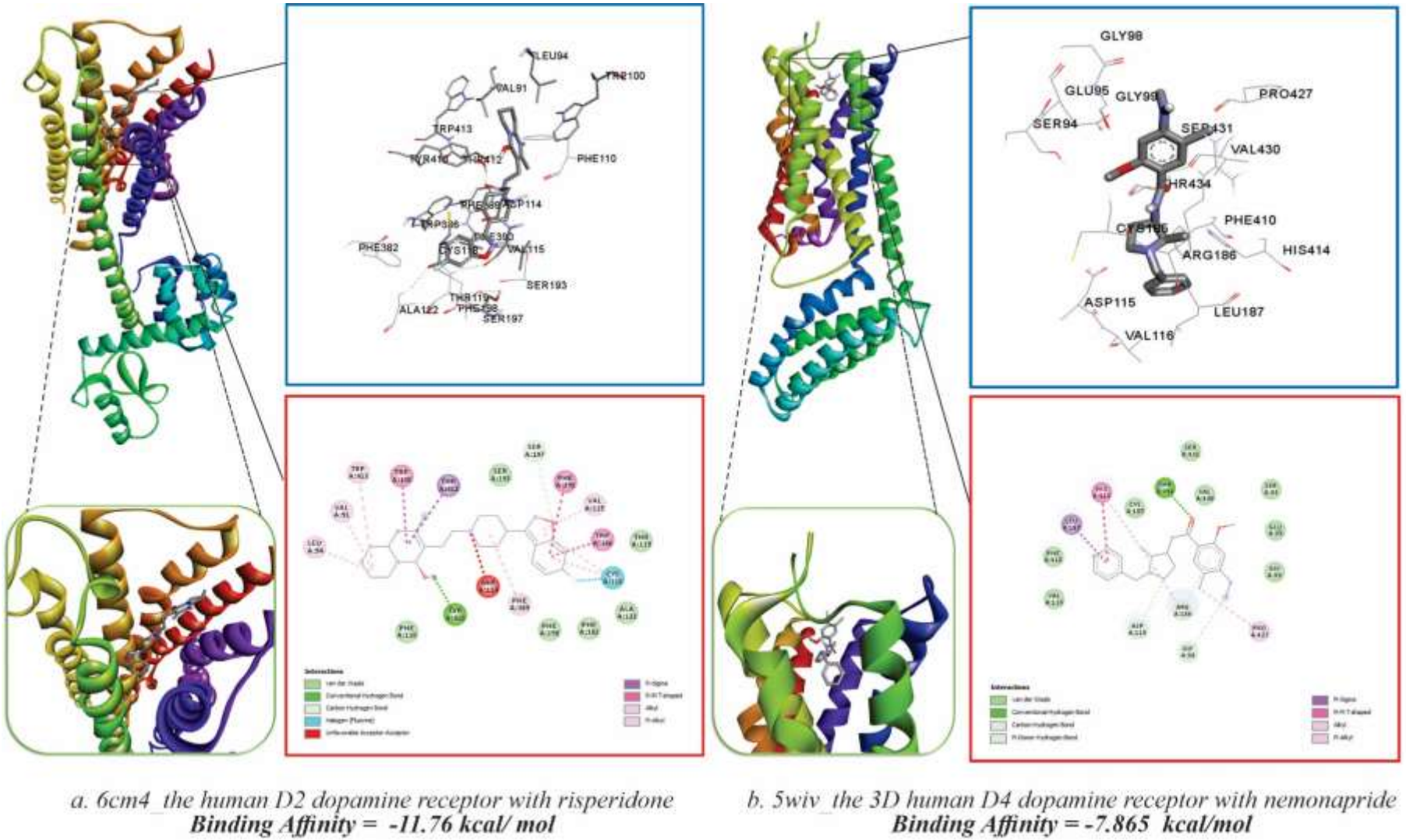
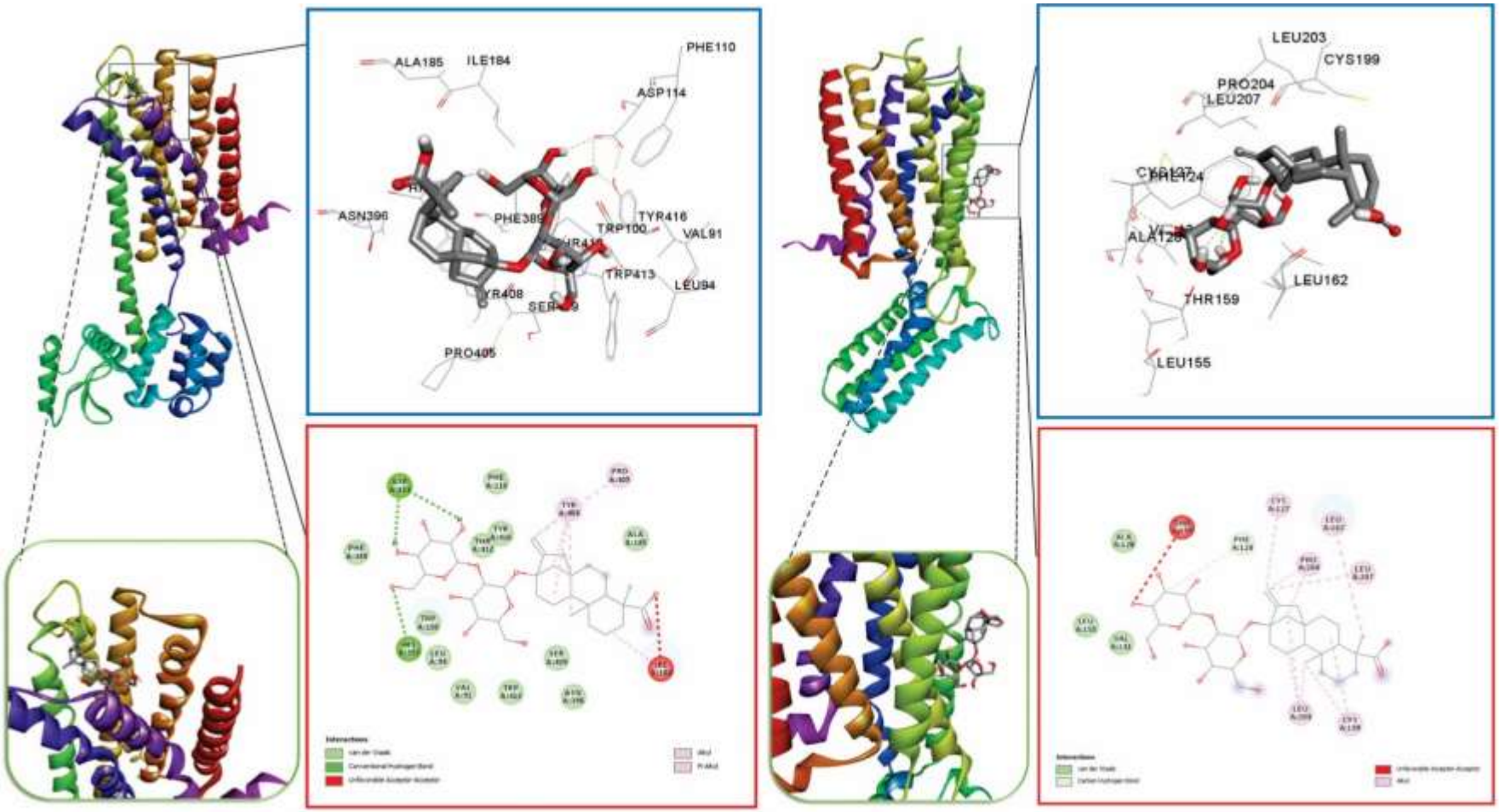


Figure 3. (a) 2D/3D Interaction of 6cm4-the human D2 dopamine receptor with Risperidone (-11.76 kcal/ mol)), (b) 2D/3D Interaction of 5mwi_the human D4 dopamine receptor with Nemonapride (-7.865 kcal/mol))



a. 6cm4_the human D2 dopamine receptor with Steviolbioside (CID16401639) ***Binding Affinity = --7.486 kcal/ mol***

b. 5wiv_the 3D human D4 dopamine receptor with Steviolbioside (CID16401639) ***Binding Affinity = -6.692 kcal/mol***

Figure 4. (a) 2D/3D Interaction of 6cm4_the human D2 dopamine receptor with Steviolbioside (CID16401639) (-7.486 kcal/ mol), (b) 2D/3D Interaction of 5wiv_the human D4 dopamine receptor with Steviolbioside (CID16401639) (-6.692kcal/mol))

The results of molecular docking of native and diterpenoid water stevia compounds are presented in Table 2. Selectivity of D2/D4 dopamine agonist/antagonist inhibitors is determined from equation (1).

D2/D4 dopamine Selectivitity = -log (Binding Affinity D4 dopamine/ Binding Affinity D2 dopamine) …..(1)

Table 2 shows the binding affinity values of each native ligand and diterpenoid compound against the D2 and D4 dopamine receptors. The selectivity value is calculated based on the binding affinities of each ligand to the D2 and D4 dopamine receptors, according to equation (1). A negative selectivity value indicates an agonist, while a positive value indicates an antagonist. Although the selectivity values of the diterpenoid compounds are negative, their 2D and 3D interaction patterns do not show similar active site positions compared to the 2D and 3D interactions of the human D4 dopamine receptor (PDB ID: 5wiv) with nemonapride. Figure 3(a) illustrates the 2D/3D interaction between D2-dopamine and its native ligand risperidone. The active site of this native ligand toward the D4 dopamine receptor includes residues ValA:91, TrpA:100, TrpA:413, ThrA:413, ValA:125, PheA:390, SerA:193, SerA:197, ThrA:119, CysA:118, AlaA:122, PheA:382, PheA:198, TrpA:386, PheA:389, AspA:114, TyrA:416, PheA:110, and LeuA:94. This active site overlaps with the binding region observed in the 2D/3D interaction of the human D2-dopamine receptor with steviolbioside (CID16401639), which involves residues PheA:389, AspA:114, PheA:110, ThrA:412, TyrA:416, TyrA:408, ProA:405, IleA:184, AlaA:185, TrpA:100, HisA:393, LeuA:94, ValA:91, TrpA:413, SerA:409, and AsnA:389, as shown in Figure 4(a). The active site further resembles that of diterpenoid ligands (e.g., rebaudioside G, sterebin F, sterebin E, sterebin G, sterebin B, sterebin M) in the 6cm4-human D2 domain, detailed in Table 2.

However, the active site and 2D/3D interaction for the native ligand nemonapride with the D2-dopamine receptor involve residues PheA:410, HisA:414, LeuA:167, CysA:185, ThrA:484, SerA:431, ValA:430, SerA:94, GluA:95, ArgA:186, GlyA:99, GlyA:98, ProA:427, AspA:115, ValA:116, and PheA:410. Crucially, none of the diterpenoid ligands from water-based stevia extracts share an active site with the native D4-dopamine ligand. Consequently, diterpenoid stevia compounds exhibit selectivity as D2-dopamine inhibitors (D2 Antagonist), including stevioside, rebaudioside B, steviolbioside, rubusoside, steviolmonoside, dulcoside A, rebaudioside A/C/E/F/G/O/R/S, sterebin A/B/D/E/F/G/I/K/M, steviol, isosteviol, austroinulin, austroinulin 6-O-acetate. And other diterpenoids 13-[(2-O-β-D-glucopyranosyl-3-O-β-D-fructofuranosyl-β-D-glucopyranosyl) oxy] kaur-16-en-18-oic acid β-D-glucopyranosyl ester; [3aR-[3α,4α(R*),6α,9α,9β]]-2,3,3a,4,5,6,6a,7,9, 9b-decahydro-9-methyl-3,6-bis(methylene)-2-oxoazuleno[4,5-b]furan-4-yl ester 2,5 dihydro-5-hydroxy-3-furancarboxylic acid; [3aR-[3α,4β(E),6α,9α,9β]]-2,3, 3a,4,5,6, 6a,7,9a,9b-decahydro-9-methyl-3,6-bis(methylene)-2-oxo azuleno[4,5-b]furan-4-yl ester 4-hydroxy-2-methyl-2-butenoic acid; [3R-(3α,3aα,4α,9α)]-3a,4,4a,7,9,9a-hexahydro-3,5,8-trimethylazuleno [6,5-b]furan-2(3H)-one; [3aR-(3α,4β, 5β,9α)]-3a,4,4a,5,6,7,8,9a-octahydro-4a,5-dimethyl-3-methylenenaphtho [2,3-b] furan-2(3H)-one; [3aR-[3α,4β(R*),9α,9β]]-2,5-dihydro-5-hydroxy-2,3,3a,4,5,7,9a,9b-octahydro-6,9-dimethyl-3-methylene-2-oxoazuleno[4,5-b]furan-4-yl ester 3-furancarboxylic acid, as showed in Table 2.

Molecular dynamics simulations were performed on key compounds steviolbioside, steviolmonoside, rebaudioside G, sterebin G, sterebin M, steviol, isosteviol, [3aR-[3α, 4β(R*),9α,9β]]-2,5dihydro-5-hydroxy-2,3,3a, 4,5,7, 9a,9b-octahydro-6,9-dimethyl-3-methylene-2-oxo azuleno[4,5-b]furan-4-yl ester 3-furan carboxylic acid, and risperidone (as a native) in the 6cm4_D2-dopamine complexes from water stevia compounds which had the main compounds and the best binding affinity in molecular docking analysis. These simulations of both complexes were carried out in the model solvents MMPBSA and MMGBSA[67] to investigate the binding interaction and the stability of the most potent compounds over the 6cm4_D2-dopamine [68]. Molecular dynamics simulations of were performed steviolbioside and risperidone_6cm4_D2-dopamine complexes, as shown Figure 5 and 6. The stability of molecular dynamics simulations is usually analyzed using two main parameters, namely RMSD (Root Mean Square Deviation) and RMSF (Root Mean Square Fluctuation). The RMSD of the protein's backbone from its initial to final conformation was used to study the stability of the protein–ligand complex. RMSD measures the average difference in the position of atoms in a molecular structure during the simulation compared to its initial position. RMSD represents the conformational changes of the molecule during the simulation time. An increasing RMSD value at the beginning of the simulation indicates that the protein structure or protein-ligand complex begins to experience conformational changes, for example the protein begins to open and the ligand seeks the right binding position. The RMSD simulation showed steviolbioside in the 6cm4_D2-dopamine got overall stability after 2 ns of MD simulation time with RMSD stabilizing at an

average of 4Å (Fig. 5B) but risperidone in the

Table 2. Binding Affinity and Selectivity's of Diterpenoid Water Stevia Extracts towards D2/D4 dopamine

Bioactive (Diterpenoid Water Stevia Extracts) and Native compounds	Binding Affinity(kcal/mol) D2/D4 dopamine Selectivity		Selectivity
	human D2 dopamine 6cm4	human D4 dopamine 5wiv	
Nemonapride	-6.532	**-7.865**	**-0.08070**
Risperidone	**-11.760**	-7.508	**0.19490**
Stevioside (CID442089)	-5.741	-6.852	-0.07683
Rebaudioside B (CID21593623)	-5.751	-6.374	-0.04467
Steviolbioside (CID16401639)	**-7.486**	-6.692	0.04869
Rubusoside (CID24721373)	-6.774	-7.414	-0.03921
Steviolmonoside (CID21593622)	-7.521	-7.705	-0.01050
Dulcoside A (CID72941582)	-6.687	-7.145	-0.02877
Rebaudioside A (CID6918840)	-6.302	-6.469	-0.01136
Rebaudioside C (CID60208888)	-6.398	-6.605	-0.01383
Rebaudioside G (CID21591681)	**-7.278**	-6.611	0.04174
Rebaudioside F (CID72941817)	-5.977	-6.597	-0.04286
Sterebin I (CID101263051)	-6.601	-6.626	-0.00164
Rebaudioside S (CID132566506)	-6.566	-6.836	-0.01750
Rebaudioside R (CID132566505)	-5.871	-6.913	-0.07095
Rebaudioside E (CID72710721)	-6.170	-6.630	-0.03123
Sterebin F (CID13996076)	**-6.446**	-6.646	-0.01327
Sterebin E (CID13996075)	**-6.638**	-6.342	0.01981
13-[(2-O-beta-D-gluco pyranosyl-3-O-beta-D-fructo furanosyl-beta-D-glucopyranosyl) oxy]kaur-16-en-18-oic acid beta-D-glucopyranosyl ester (CID101623749)	-4.928	-5.606	-0.05598
Sterebin G (CID13996077)	**-7.600**	-6.557	0.06411
Sterebin B (CID71694414)	**-6.175**	-5.859	0.02281
Sterebin M (CID21589507)	**-7.346**	-6.590	0.04717
[3aR[3α,4α(R*),6α,9α,9β]]2,3,3a,4,5,6,6a,7,9, 9b deca hydro-9-methyl-3,6-bis (methylene)-2-oxoazu leno[4,5-b] furan-4-yl- ester-2,5-dihydro-5-hydroxy-3-furan carboxylic acid (CID162934623)	**-7.923**	-7.341	0.03313
Sterebin A (CID21681091)	**-7.294**	-6.467	0.05226
Sterebin K (CID21589505)	**-6.393**	-6.663	-0.01797
Steviol (CID452967)	**-7.633**	-7.245	0.02266
Isosteviol (CID99514)	**-7.419**	-8.202	-0.04357
Rebaudioside O (CID92023639)	-6.262	-5.434	0.06159
Austroinulin 6-O-acetate (CID131752054)	**-6.856**	-6.613	0.01567
[3aR-[3α,4βE),6α,9αa, 9β]]2,3,3a,4,5,6,6a,7,9a,9b deca hydro-9-methyl-3,6bis (methylene)-2-oxoazu leno [4,5-b] furan-4-yl ester-4-hydroxy-2-methyl 2-butenoic acid (CID13994647)	**-7.049**	-6.724	0.02050
Sterebin D (CID14396288)	-6.114	-6.194	-0.00565
Austroinulin (CID11472742)	-6.153	-6.613	-0.03131
[3R-(3α,3α,4α,9α)]-3a,4,4a,7,9,9a-hexahydro-3,5,8-trimethylazuleno [6,5b]furan-2(3H)-one (CID162900224)	**-8.559**	-7.034	0.08522
[3aR-(3α,4β,5β,9α)]-3a,4,4a,5,6,7,8,9a-octahydro-4 a,5-dimethyl-3-methylenenaphtho [2,3-b]furan-2(3H)-one (CID91704079)	**-7.340**	-6.776	0.03472
[3aR-[3α,4β(R*),9α, 9β]]-2,5dihydro-5-hydroxy-2,3,3a,4,5,7, 9a,9b-octahydro-6,9-dimethyl-3-methylene-2-oxoazuleno[4,5-b]furan-4-yl ester 3-furan carboxylic acid (CID162977543)	**-9.375**	-7.002	0.12675

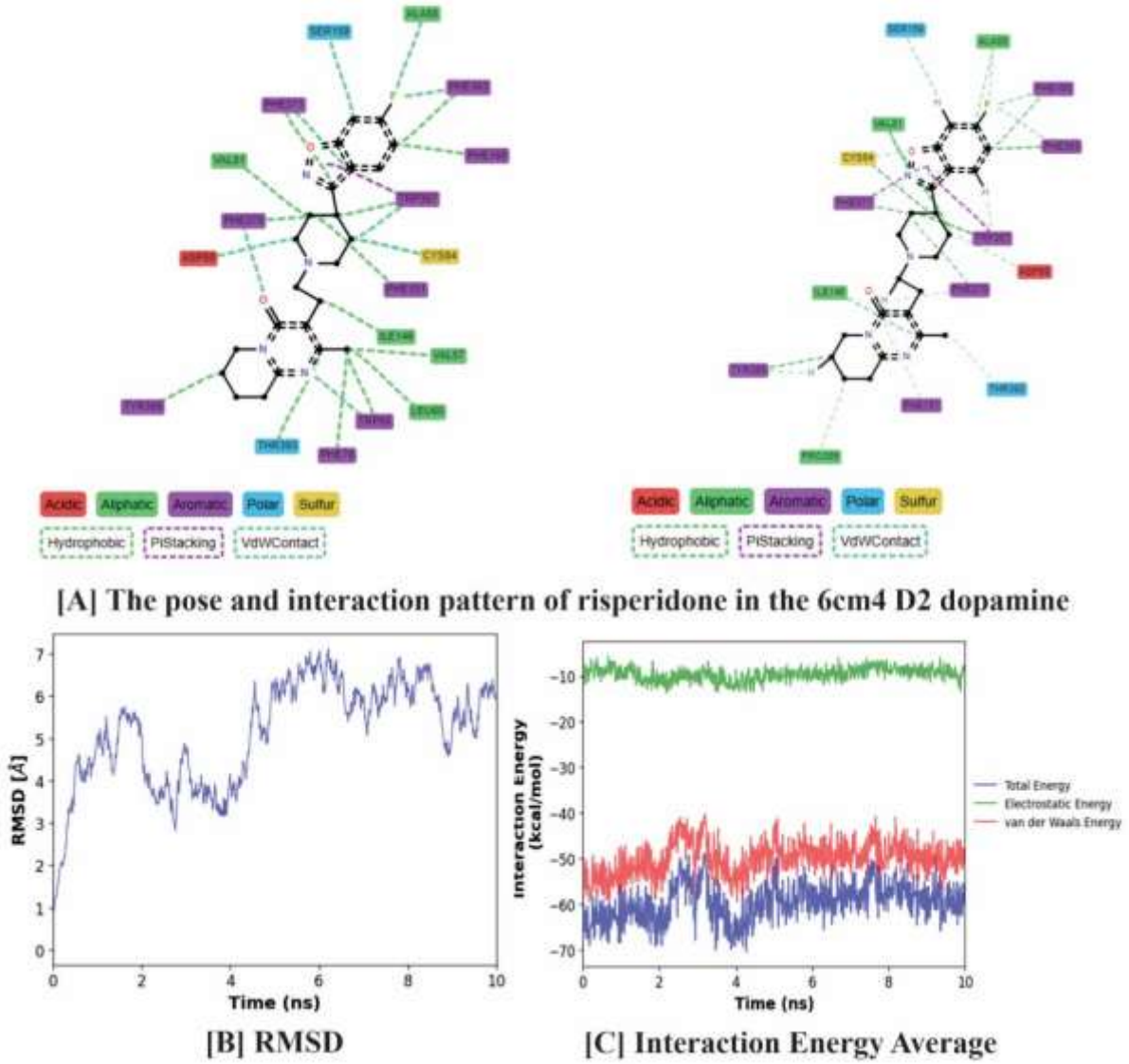


Figure 5. Molecular dynamic simulation, RMSD and interaction energy average of risperidone (native) in the 6cm4_D2-Dopamine complexes

6cm4_D2-dopamine got overall stability after 2 ns of MD simulation time with RMSD stabilizing at an average of 5.5Å (Fig. 6c). These results indicated that the steviolbioside in the 6cm4_D2-dopamine was more stable compared to risperidone in the 6cm4_D2-dopamine during the simulation time. The RMSD value is stable and constant, this indicates that the molecule has reached a stable conformation and maintains its position during the simulation.

In other words, the protein-ligand structure is already in equilibrium and stable. A small and stable RMSD value (e.g. around 0.2 nm or 2 Å) indicates the stability of the molecular structure during the simulation [(68)]. RMSF measures the fluctuation of the positions of atoms or amino acid residues individually during the simulation, thus providing an overview of the local flexibility or movement of certain parts of the protein. A low RMSF value at a certain residue indicates that the part is relatively stable and less mobile, which means that the ligand interaction with the residue is quite stable. Conversely, a high RMSF value indicates large fluctuations and that part of the protein is more flexible or unstable. Thus, RMSF is used to identify the most flexible part of the protein during the simulation and assess the stability of protein-ligand interactions at the residue level. Based on the timeline results (Fig 5D), resperidone effectively involved in the interaction with the dopamine D2 binding site. Risperidone interacts with residues in the active site and domain B, reducing friction in these regions. Similarly, to the timeline, Fig 6D, steviolbioside also interacts with residues in the active site and D2 domain of dopamine, leading to a reduction in readout in these areas..

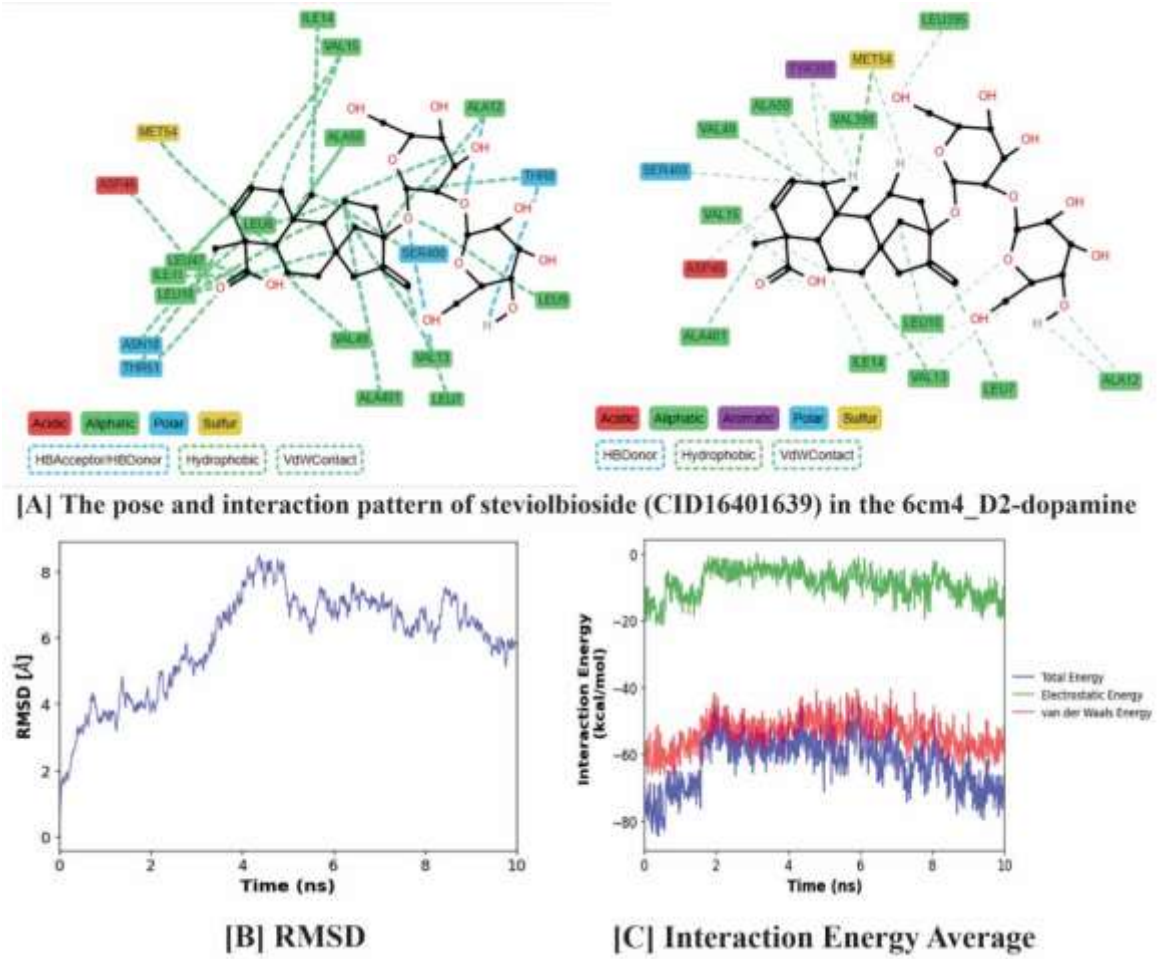


Figure 6. Molecular dynamic simulation, RMSD and interaction energy average of steviolbioside (CID16401639) in the 6cm4_D2-Dopamine complexes

The figure also depicts the timeline of interactions between the steviolbioside moiety and the D2 active site of dopamine during simulations.\The overall stability observed in the simulations, including minimal fluctuations and sustained key contacts, suggests that steviolbioside can reliably bind the D2 receptor, supporting its candidacy as a dopamine D2 receptor antagonist.

In molecular dynamics (MD) simulations, the interaction energy between molecules and ions the same stability, as presented in Table 3. Furthermore, Fig. 5A and 6A illustrates the timeline interactions of the risperidone and steviolbioside moiety of 6cm4_D2-dopamine with its active sites of the simulation time. In the research, binding energy calculation in molecular dynamic simulation of risperidone and steviolbioside in the D2 dopamine using MMPBSA and MMGBSA solvent model. Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) and Molecular Mechanics/Poisson−Boltzmann Surface Area (MM/PBSA) are computational methods that calculate binding free energies for macromolecules. is calculated using electrostatic energy and van der Waals interactions. The energy of these interactions can be calculated using the particle mesh-Ewald (PME) method or by setting a cutoff radius [69-71]. Based on the timeline result, steviolbioside more effectively participated in interactions with the 6cm4_D2-dopamine binding site (Fig. 5B). Likewise, diterpenoid compounds in water stevia extracts, such as steviolmonoside, rebaudioside G, sterebin G, sterebin M, steviol, isosteviol also have They are popular methods for predicting binding free energy because they are more accurate than molecular docking scoring functions but less computationally demanding than alchemical free energy methods[72]. MMPBA Binding energy of steviolbioside in the 6cm4_D2-dopamine (ΔG) -43.3501 ± 6.5046 kcal/ mol. MMGBSA Binding energy steviolbioside in the 6cm4_D2-dopamine (ΔG) 2.0977 ± 8.1381 kcal/mol. The difference Binding energy value, between MMPBSA and MMGBSA are MM/GBSA including polar and nonpolar contributions to ΔG and MMPBSA including Bond, angle, and dihedral energies,

electrostatic energies, van der Waals energies, polar and nonpolar contributions to ΔG, and ΔTΔS[73-75]. Binding energy of steviolmonoside, rebaudioside G, sterebin G, sterebin M, steviol, isosteviol, and resperidone, as shown Table 3. Apart from that, the binding energy value of steviolbioside in the 6cm4_D2-dopamine is more stable, this is in line with the RMSD and interaction energy average values. As well as, steviolmonoside, rebaudioside G, sterebin G, sterebin M, steviol, isosteviol, and respeidone, but [3aR-[3α,4β(R*),9α,9β]]-2,5-dihydro-5-hydroxy-2,3,3a,4,5,7,9a,9b-octahydro-6,9-dimethyl-3-methylene-2-oxoazule-no[4,5b]furan-4-yl ester 3-furan carboxylic acid unstable.

Table 3. Interaction Energy and Binding Energy Ligand Diterpenoid to human D2 dopamine.

Bioactive (Diterpenoid groups) and Native / Ligand compounds	Interaction Energy Average (kcal/ mol)	Binding Energy Ligand (kcal/mol) in human D2 dopamine (id:6cm4)	
		MMGBSA	MMPBSA
Risperidone (Native)	-59.55 ± 4.02	-37.7570 ± 2.8024	4.6235 ± 4.9522
Steviolbioside (CID16401639)	-62.53 ± 7.83	-43.3501 ± 6.5046	2.0977 ± 8.1381
Steviolmonoside (CID21593622)	-73.69 ± 3.52	-45.6881 ± 3.6053	4.9080 ± 2.6586
Rebaudioside G (CID21591681)	**-83.58 ± 7.37**	**-51.8741 ± 7.0859**	16.0145 ± 9.5461
Sterebin G (CID13996077)	-45.94 ± 3.10	-36.5222 ± 2.6371	-8.2642 ± 3.6328
Sterebin M (CID21589507)	-45.00 ± 3.50	-36.9483 ± 2.7704	-7.6042 ± 2.8818
Steviol (CID452967)	-52.87 ± 2.56	-44.6738 ± 2.8618	**-10.1216 ± 4.5406**
Isosteviol (CID99514)	320.39 ± 14.24	326.9446 ± 15.3852	346.9858 ± 16.4284
[3aR-[3α,4β(R*),9α, 9β]]-2,5dihydro-5-hydroxy-2,3,3a,4,5,7, 9a,9b-octahydro-6,9-dimethyl-3-methylene-2-oxoazuleno[4,5-b]furan-4-yl ester 3-furan carboxylic acid (CID162977543)	-19.64 ± 4.19	Unstable	Unstable

The molecular docking studies and dynamic simulations carried out in this research strongly support the hypothesis through several important findings. The diterpenoid compounds show a clear preference for binding to D2 receptors over D4 receptors. Although some compounds also interact with the D4 receptor (PDB: 5wiv), their binding sites differ from those of the native ligand[76]. The highest binding affinity and greatest stability are observed with the D2 receptors, which is consistent with the established therapeutic targets for schizophrenia. Notably, compounds such as steviolbioside, steviolmonoside, and sterebin G demonstrate strong binding to the active site of the D2 receptor (PDB: 6cm4), effectively competing with the natural ligand. In several cases, the binding affinity of these diterpenoid compounds matches or even exceeds that of the native ligand. Furthermore, molecular dynamics simulations confirm the stability of the complexes formed between stevia compounds and the D2 receptor, indicating a consistent antagonistic potential and suggesting reliable therapeutic efficacy over time[77].

The therapeutic implications for treating insomnia associated with schizophrenia involve complex, multi-faceted mechanisms. Stevia diterpenoids mediate D2 receptor antagonism, which reduces excessive dopamine activity and effectively disrupts the pathological cycle of sleep disturbances characteristic of schizophrenia-related insomnia[78]. This decrease in dopamine levels also facilitates the normalization of melatonin production, leading to the restoration of circadian rhythms and improvement in sleep architecture and patterns[79]. In addition to these effects, the antioxidant properties of stevia compounds help reduce oxidative stress in the brain, thereby supporting neuronal integrity and promoting overall brain health[80].

Previous research on stevia water extract containing diterpenoids has demonstrated notable capabilities in modulating dopaminergic activity. In vivo studies using mouse models revealed that stevia administration increased dopamine levels in the cortex while simultaneously decreasing dopamine concentrations in the striatum, indicating a sophisticated, region-specific modulation of dopamine that may offer therapeutic advantages [77]. Additionally, clinical case reports have linked stevia extract consumption to restless legs syndrome (RLS), a neurological disorder associated with dopamine dysfunction, thereby reinforcing stevia's influence on dopaminergic pathways and suggesting its potential therapeutic value[81]. Beyond dopamine modulation, stevia also exhibits significant antioxidant and membrane-stabilizing properties within the central nervous system, which may protect neurons from oxidative damage commonly associated with psychiatric disorders, thus providing further therapeutic benefits[80]. Therefore, the

convergence of computational modeling data, in vivo experimental results, and clinical observations collectively build a strong scientific basis to consider stevia as a promising new therapeutic agent for schizophrenia-related sleep disorders through targeted dopamine receptor modulation. *In silico* analysis with a dopamine D2/D4 selectivity approach, this study is expected to provide new insights into the mechanism of action of ditepenoid compounds and even other natural compounds and their contribution as safer and more effective therapeutic candidates. The results of this study are also expected to provide significant contributions to the development of new therapies that reduce the side effects often associated with synthetic drugs for schizophrenia and insomnia [82]. This *in silico* analysis data will be continued to be confirmed with the IC_{50} value in in-vitro and in-vivo analysis until its clinical research [83]. Stevia-derived diterpenoids are the primary focus as dopamine D2 receptor antagonists in the therapy of insomnia and schizophrenia. However, other bioactive compounds present in the stevia plant include flavonoids and phenols, which also exhibit significant biological activities such as antioxidant, anti-inflammatory, and immunomodulatory effects. Several studies have shown that stevia contains various phenolic acids, including chlorogenic acid and isochlorogenic acid, as well as flavonoids such as quercetin, luteolin, and kaempferol, which may contribute to the pharmacological effects of the plant. The phenols and flavonoids in stevia support nervous system health and possess potential neuroprotective effects that could complement the therapeutic effects of diterpenoids. Therefore, while this article focuses on diterpenoids, the presence of flavonoids and phenols warrants further research to complement and potentially enhance the overall therapeutic effects.

Conclusion

In silico analysis using the D2/D4 dopamine selectivity approach indicates that diterpenoid compounds found in water stevia extracts, such as steviolbioside, steviolmonoside, rebaudioside G, sterebin G, sterebin M, steviol, and isosteviol have the potential to act as D2 dopamine receptor antagonists. This suggests their possible application in targeting the therapeutic mechanism for schizophrenia-related insomnia.

Acknowledgment

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics Statements

Our research does not require ethical approval from the ethics committee in accordance with research integrity regulations in our country, because we have not yet conducted in-vivo and clinical research.

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