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The Compound Profile of *Chrysanthemum cinerariifolium (Trev.)* Extract and Its Potential in Inhibiting COX-2 and CDK-4/6 Receptors in *Oral Squamous Cell Carcinoma* (OSCC) (*In Silico Study*)

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Keyword :
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A b s t r a c t

Cancer is a disease that appears characterized by abnormal cell growth which can then infect adjoining parts of the body and or spread to other organs. One type of cancer that often occurs is Oral Squamous Cell Carcinoma (OSCC). There are several target receptors involved in cell proliferation, which are COX-2 and CDK-4/6 receptors. One of the herbal treatments for OSCC can be done using Chrsanthemum cinerariifolium (Trev.) herb extract. This research aims to find active compounds in Chrysanthemum cinerariifolium (Trev.) using UPLC-QToF-MS/MS method, the analysis of physiochemical prediction, toxicity analysis and molecular docking results on the proteins of COX-2 and CDK-4/6. This research combines two types of research, which are descriptive experimental for metabolite analysis and preexperimental one shot case study type for in silico test. The analysis of Metabolite compounds is using UPLC-QToFMS/MS Instrumentation, and for in silico tests using some SwissADME for physiochemical tests, PkCSM and Protox Online Tools for toxicity tests and Biovia Discovery Studio Visualizer and PyRx 0.8 for molecular docking tests. The results of this study obtained 28 compounds from metabolite profiling. And the results of molecular docking showed 1 compound with the best affinity on the tethering of both receptors. The compound is Diosmetin. There are also amino acid with 15 residues obtained in this process. However, the bonding value of native ligand with target protein is higher than the bonding of test ligand with target protein.

Kata kunci :
Chrysanthemum cinerariifolium (Trev.), Metabolite Profiling, Molecular Docking, Oral Squamous Cell

A B S T R A K

Kanker merupakan suatu penyakit yang muncul dengan ditandai adanya pertumbuhan sel abnormal yang kemudian dapat menyerang bagian tubuh yang berdampingan dan atau menyebar ke organ lain. Salah satu jenis kanker yang sering terjadi yaitu Oral Squamous Cell Carcinoma (OSCC). Ada beberapa target reseptor yang terlibat dalam proliferasi sel yaitu reseptor COX-2 dan CDK-4/6. Salah satu pengobatan herbal untuk OSCC bisa dilakukan menggunakan ekstrak herba *Chrsanthemum cinerariifolium (Trev.)*. Penelitian ini bertujuan untuk menemukan senyawa aktif pada *Chrysanthemum cinerariifolium (Trev.)* menggunakan metode UPLC-QToF-MS/MS, analisis prediksi fisiokimia, analisis toksisitas serta hasil molecular docking pada protein COX-2 dan CDK-4/6. Penelitian ini menggabungkan dua jenis penelitian yaitu deskriptif eksperimental untuk analisis metabolit dan jenis pre eksperimental one shot case study untuk uji in silico. Analisis metabolit senyawa menggunakan Instrumentasi UPLC-QToFMS/MS, dan untuk uji in silico menggunakan beberapa SwissADME untuk uji fisiokimia, PkCSM dan *Protox Online Tools* untuk uji toksisitas serta *Biovia Discovery Studio Visualizer* dan PyRx 0.8 untuk uji molecular docking. Hasil dari penelitian ini didapatkan sebanyak 28 senyawa hasil metabolite profiling. Dan hasil *molecular docking* menunjukkan 1 senyawa dengan afinitas terbaik pada penambatan kedua reseptor. Senyawa tersebut adalah Diosmetin. Dan juga terdapat sebanyak 15 residu asam amino yang didapatkan pada proses ini. Akan tetapi, nilai ikatan yang terjadi pada native ligand dengan protein target lebih tinggi jika dibandingkan dengan ikatan ligan uji dengan protein target.

INTRODUCTION

Cancer is a disease that appears characterized by abnormal cell growth which can then invade adjacent body parts and or spread to other organs.[1] Cancer is one of the diseases that is not contagious.[1] *Oral Squamous Cell Carcinoma* (OSCC) is one of the most common types of cancer worldwide with a higher incidence rate in men than women.[2] *Oral Squamous Cell Carsinoma* (OSCC) is a type of malignant tumor originating from epithelial tissue that is able to infiltrate through the bloodstream and lymphatic flow and can spread throughout the body.[3]

In the carcinogenesis process, dysregulation of cell cycle control is an important requirement. The cell cycle is regulated by serine threonine kinase proteins called Cyclin- Dependent Kinase (CDK). These proteins regulate various steps of cell cycle progression by phosphorylating many substrates, namely the nuclear lamina. This regulatory mechanism forms a checkpoint that can be stopped after cell damage to allow repair and maintain cell integrity or alternatively to eliminate mutated and potentially harmful cells. Currently, there is evidence that prostaglandins produced by COX-2 intervene in tumor cell proliferation as NSAIDs and COX-2 inhibitors selectively inhibit the proliferation of various types of cancer cells that express COX-2.[4]

Until now, various cancer medications have been used, such as surgery and chemotherapy. However, both treatments have high toxicity and harmful side effects.[5] People's concerns about the negative side effects of cancer medical treatment may encourage patients to seek traditional medication. Herbal plants widely used as traditional medicine have many benefits, such as the white chrysanthemum plant (*Chrysanthemum cinerariifolium (Trev.)),* which is an herbal plant belonging to the genus *Chrysanthemum* and the *Asteraceae* family.[6] The use of herbal plants as an effort to treat Oral Squamous Cell Carcinoma still needs to be explored, researched and developed and further optimized as herbal medicines.

Chrysanthemum cinerariifolium (Trev.) or commonly known as white chrysanthemum flower is a type of plant that has many medicinal properties such as anti-cancer, anti-bacterial, anti-inflammatory, and also anti-mutagenic. The anti-cancer effect of the plant *Chrysanthemum cinerariifolium (Trev.)* is owned by flavonoid compounds and also quercetin. In this research utilizing herbs (combined extracts of stem, leaf, and flower parts), metabolite profiling extracts conducted using UPLC-QToF-MS/MS method. Then to find the activity of the results of metabolite profiling compounds and predict the potential of pharmaceuticals in plants is to use in silico methods.[7] One of the in silico methods used in this study is *molecular docking*.[8]

METHODS

1. Materials

The tools used in the metabolite profiling process are a set of UPLC-QToF-MS/MS instrumentation. Meanwhile, the tools used in the *molecular docking* process are Toshiba GS40026 Intel(R) Core(TM) i3-4005U CPU @1.70GHz, *Microsoft Office Excel* 2019, software (MassLynx, PyRx 0.8 Autodock Vina method, *Biovia Discovery Studio Visualizer* 2021, PkCSM), and databases (ChemSpider, PubChem, Protein Data Bank, UniProt, *Swiss*ADME). The materials used in the metabolite profiling process are herbs from the *Chrysanthemum cinerariifolim (Trev.)* plant which are the result of extracts from the stems, leaves, and flowers of the chrysanthemum plant, 96% ethanol, distilled water, ethyl acetate, water eluent, acetonitrile formic acid, tissue, aluminum foil and filter paper, as well as 3D structures of COX-2 with protein code 3LN1 and CDK-4/6 with protein code 5L2I obtained from www.rscb.org.

2. Plant Determination

Chrysanthemum cinerariifolium (Trev.) plants obtained from Punten Village, Batu City, East Java then carried out a determination step at UPT Materia Medica Batu, East Java, Indonesia with license number: 074/153/102.20-A/2-22 to ensure that the sample used is correct.

3. Extraction

The initial preparation stage is to sort the *Chrysanthemum cinerariifolium (Trev.)* plants that are deemed suitable for use. Then, each part is cut and the parts that are still good and fresh are taken. Next, they are washed and dried, then made into herbal powder. The herb powder *of Chrysanthemum cinerariifolium* (Trev.) obtained was then put into an erlenmeyer and added 96% ethanol in a ratio of 1:20. The mixture was extracted using UAE (*Ultrasonication Assisted Extraction*) for 2 minutes with three replicates. Furthermore, the filtrate evaporated using a rotary evaporator at 500 C to produce a raw extract and concentrated using an oven at 400 C until the texture of the extract becomes concentrated.

4. Sample Preparation for Metabolite Profiling Analysis

The first step of a metabolite profiling procedure is the sample preparation. Sample preparation must be done first before being injected into the UPLC-MS instrument. The type of method used in this sample's preparation is *Solid Phase Extraction* (SPE). The dry fraction was weighed as much as 10 mg and dissolved into a volumetric flask with 10 mL of solvent and then inserted into the conditioned SPE column. The organic material left in the column was eluted with 10 mL of methanol. The methanol filtrate was collected and then continued with elution using 10 mL of dichloromethane, the dichloromethane filtrate was then collected until there was a methanol filtrate and dichloromethane filtrate in a separate vessel.

5. Prediction of Psysiochemica Properties

The 2D structure of 25 compounds obtained from the results of the description using the Chemdraw application was then converted into Cannonical SMILES code using *Swiss*ADME. After completing these steps, compounds were obtained that fulfilled the Lipinski Rule of Five (RoF) and also assessed for grades of TPSA (Topological Polar Surface Area), GI Absorbtion, BBB Permeant, and P-GP Substrate.[9,10,11]

6. Toxicity Prediction

The 25 compounds that have been converted into Cannonical SMILES format were then processed using the pkCMS online tool (https://biosig.lab.uq.edu.au/pkcsm) to predict the pharmacokinetic and toxicity properties of the compounds. The parameters used in this toxicity prediction are Ames Toxicity, Hepatotoxicity, and LD50.[12,13]

7. In Silico Sample Preparation

Native ligands and test ligands derived from compounds from *metabolite profiling* of *Chrysanthemum cinerariifolium* (Trev.) extracts that have been screened for physiochemical properties and have been tested for toxicity levels are then geometry optimized first using Avogadro software to obtain the most stable geometry structure of the chemical structure before adding compounds to the target .[14]

8. Receptor Preparation

The Receptors used in this study was selected from the *protein data bank* with ID code 3LN1 for celecoxib and 5L2I for palbociclib. The selection of receptor with ID 3LN1 is because the receptor contains CEL macromolecules which are the target of research with *native ligand* celecoxib. Similarly, the selection of receptor 5L2I was chosen because it contains the macromolecule LQQ targeted at the *native ligand* palbociclib in this study.

9. Internal Validation of *Molecular Docking*

Internal validation is used to determine whether the program used for *molecular docking* meets the requirements or not.

Internal validation in molecular docking is done by *re-docking* between the default ligand of the target receptor using PyRx 8.0 software Vina *Autodock Tools* method. The analysis used to evaluate the validation results is the RMSD value, the binding site found and the parameters used are considered valid if the RMSD ≤ 2Å.[15]

10. Molecular Docking of Test Ligand Against Receptor

Molecular docking was performed on 25 compounds resulting from metabolite profiling. of *Chrysanthemum cinerariifolium* (Trev.) herb extract against Cyclooxigenase-2 (COX-2) and Cyclin Dependent Kinase-4/6 (CDK-4/6) receptors using *Pyrx software*. 8.0 and Biovia *Discovery Visualizer 2021 software*.

RESULT

Metabolite Profiling Compound Analysis Results

The results obtained from the UPLC-QToF-MS/MS instrument are in the form of chromatograms with compounds that appear early in the peak chromatogram are polar and then will increasingly decrease the level of polarity in subsequent peaks. In this MS system, the analyte will then go through three stages, which are the gas phase, the ion phase, and also the separation of ions based on their respective mass to charge ratios (M/Z). The results of the ion separation process will then be detected by the detector system and will be visualized in the form of a chromatogram and processed using masslynx software version 4.0 which then displays the m/z spectra of each peak on the chromatogram. Each chromatogram peak indicates the presence of one compound. From the chromatogram, 28 peaks were obtained which were then predicted the molecular formula of the compound. The chromatogram results and metabolite profiling compounds are shown in Figure 1 and Table 1.

Physiochemical Properties Screening Results

The results of the screening of physiochemical properties that have been carried out on *native ligand* and 25 compounds of metabolite profiling results are in the accumulation table and *Swiss*ADME webtool will display in the form of Boiled-EGG. In addition to the Lipinski Rules of Five, other criteria met are Topological Polar Surface Area (TPSA), Torsion, Human Intestinal Absorbtion (HIA) parameters consisting of (Gastrointestinal Absorbtion and Blood Brain Barrier Peremant) and the last is P-GP Nonsubstrate). From the screening results that have been carried out on native ligands along with 25 compounds from metabolite profiling of *Chrysanthemum cinerariifolium (Trev.)* herb extracts, 8 compounds were found to meet the Lipinski Rules of Five (RoF) and these results are shown in table 2

Prediction of Toxicity

Toxicity parameters used in this study are Amestoxicity, Hepatotoxicity, and LD50. Based on Globally Harmonized System (GHS), the toxicity level is divided into class I to VI. Toxicity classes use LD threshold amounts of 5, 50, 300, 2000, and 5000 mg/kg body weight. The results of toxicity prediction are shown in the table 3. The screening results for Human Intestinal Absorbtion (HIA) and P-GP Non-Substrate parameters are shown in figure 2

DISCUSSION

Analysis the Result of Metabolite Profiling with UPLC_QToF-MS/MS

The results of the chromatogram data were interpreted as presented in Figure 1 and Table 1, which shows the results of 28 peaks obtained, the peak that has the highest abundance is the peak with a retention time of 11.83 minutes. At the peak with retention time of 11.83 minutes with an area of 12.70% showing molecular ions m/z 270.1859 measured mass and calculated mass based on chemdraw is 270.1858. The value of both shows a suitability. It can be said to be appropriate

if the measured mass and calculated mass values give the same results or have a difference of less than 0.0005. So that the molecular formula of the compound is C18H23NO with the compound name, orphenadrine. Based on the speculation of compounds found in herbal extracts of *Chrysanthemum cinerariifolium (Trev.)*, compounds are obtained that have the same type as found in other plants that have been tested for activity and have even been processed into a medicinal product in the health or pharmaceutical field. From several compounds of metabolite profiling results of *Chrysanthemum cinerariifolium (Trev.)* herb extracts, several compounds were obtained that were the same in other plants and had been done in previous research.

Compounds that have anti-cancer activity include Vitexin, Diosmetin compounds, Jaceosidine works in inducing cell apoptosis[16], (±)-Usnic acid[17], Orphenadrine and also Linoleamid compounds that have been proven to treat colorectal cancer (http://chemspider.com). Addition to these anti-cancer compounds, there are several compounds that are antioxidants including Diosmetin compounds[16], (±)-Usnic acid[17], also Retusin (Flavonol)[18]. And the last compound properties related to this research are the anti-inflammatory compound properties obtained in several compounds: Diosmetin[19], Jaceosidin[20], Nabumetone[21], (±)-Usnic acid[17], and the last is the Retusin (Flavonol)[18].

Prediction of Physiochemical Properties

The results of screening compounds that passed the screening of physiochemical properties and can be continued to the in silico process using *molecular docking* method have been shown in table 2. The chemical physiochemical analysis carried out first by seeing whether the compound has met the rules of *Lipinski Rules of Five* (RoF), *Tological Polar Surface Area*, *Torsion, Human Intestinal Absorbtion* (HIA) parameters and also P-gp non-substrate.

The final results obtained from the screening of the two *native ligands* (comparison compounds) have met the rules, while from the metabolite profiling compounds obtained as many as 8 compounds that have met the rules and these compounds include 1,2-di-O-methyl-4-[(2R)-2,4- dihydrobutyramido]-4,6-dideoxy-α-D-mannopyranoside, DL-Phenylalanine, Diosmetin, Jaceosidin, (±)-Usnic acid, Olemelin, Retucine (flavonol).

Prediction of Toxicity Properties

The results of the toxicity test in this study using the PkCSM Online Tools website both *native ligands*, which are celecoxib and palbociclib, are predicted to be non-toxic because they are in class 4 and 5 classifications respectively. Amestoxicity test results both show the results that the drug is not mutagenic but both can cause toxicity to the hepar. Compound metabolite profiling results of *Chrysanthemum cinerariifolium* (Trev.) herb extract specifically on 8 compounds that passed the screening of physiochemical properties, there are as many as 3 compounds that fall into class IV and 5 other compounds fall into class 5. The compounds L-(+)-Valinol, 1,2-di-O-methyl-4-[(2R)-2,4-dihydrobutyramido]-4,6-dideoxy-α-D- mannopyranoside, Diosmetin, Jaceosidine, Olmelin and Retucine are not mutagenic, not toxic to the hepar. For the compound DL-Phenylalanine is non-toxic but shows toxic properties to the hepar. As for the compound (±)-Usnic acid, this compound is mutagenic and toxic to the hepar. It is known that the compounds that have been classified into classes IV, V, and VI are compounds that are at a low level of toxicity. The higher the value shown in the LD50, the safer the compound will be if it enters the human body compared to compounds with a small LD50 value and the compound is declared toxic if it enters classes I, II, and III.[13]

Molecular Docking Results and Amino Acid Interactions

Based on the results of *molecular docking* of compounds from metabolite profiling of *Chrysanthemum cinerariifolium* (Trev.) herb extract, 3 ligand compounds were obtained from a total of 8 compounds that passed the physiochemical screening using SwissADME webtool. According to the 3L2I receptor, the three compounds form key hydrogen bonds on key amino acid residues namely Leu338, Gln178, Phe504, His75 and Arg499. The ligands include DL- Phenylalanine, Diosmetin, Retucine. While the results of molecular docking against 5LN1 receptors also obtained as many as 3 compounds that have passed the *molecular docking* results from a total of 8 compounds that passed the screening of physiochemical properties and toxicity tests. These compounds include 1,2-di-O-methyl-4-[(2R)-2,4-dihydrobutyramido]-4,6-dideoxy-α-D-mannopyranoside, Diosmetin, and Jaceosidine. All three have the same key amino acids as the *native ligand*, which are Val101, and Asp163 and have pharmacophore distances that meet the criteria. All test compounds that passed the screening had the same amino acid bonds as the native ligand and the comparison compounds. The similarity of amino acids bound by test compounds with comparator compounds and native ligands indicates that these compounds are expected to have the same activity as comparator compounds and native ligands, this is because amino acids are active sites on receptors.

CONCLUSION

The research can be concluded that there are 28 compounds contained in the metabolite profiling of Chrysanthemum cinerariifolium (Trev.) herb extract using UPLC-QToF-MS/MS method. The active compound contained in Chrysanthemum cinerariifolium (Trev.) which has the best affinity to Cyclooxigenase-2 (COX-2) and Cyclin Dependent Kinase-4/6 (CDK-4/6) as a receptor is Diosmetin compound. There were also 15 types of amino acids contained in each bond including Glutamine (Gln), Leucine (Leu), Histidine (His), Tyrosine (Tyr), Arginine (Arg), Alanine (Ala), Methionine (Met), Valine (Val), Serine (Ser), Isoleucine (Ile) Phenylalanine (Phe), Aspartic acid (Asp), Alanine (Ala), Glutamic acid (Glu), and Lysine (Lys). However, the ratio of the bond that occurs between the ligand and the receptor and the bond that occurs between the native ligand and the receptor is higher than the ligand bond (compounds from metabolite profiling of Chrysanthemum cinerariifolium (Trev.) herb extract). Therefore, these compounds can be candidates for Oral Squamous Cell Carcinoma (OSCC) drugs based on natural ingredients

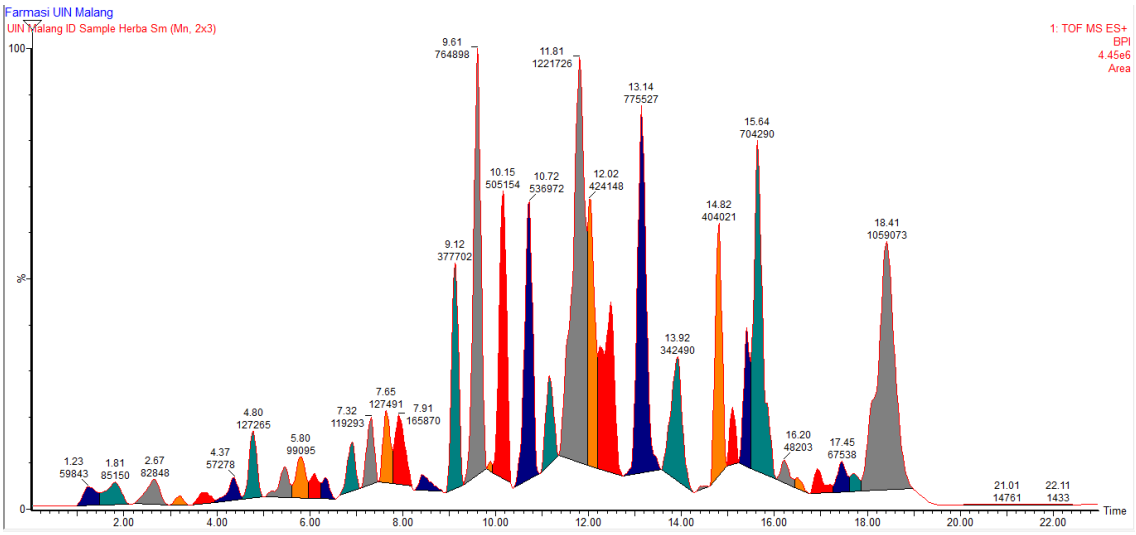

Figure 1. UPLC-QToF-MS/MS chromatogram of Chrysanthemum cinerariifolium (Trev) herb extract.

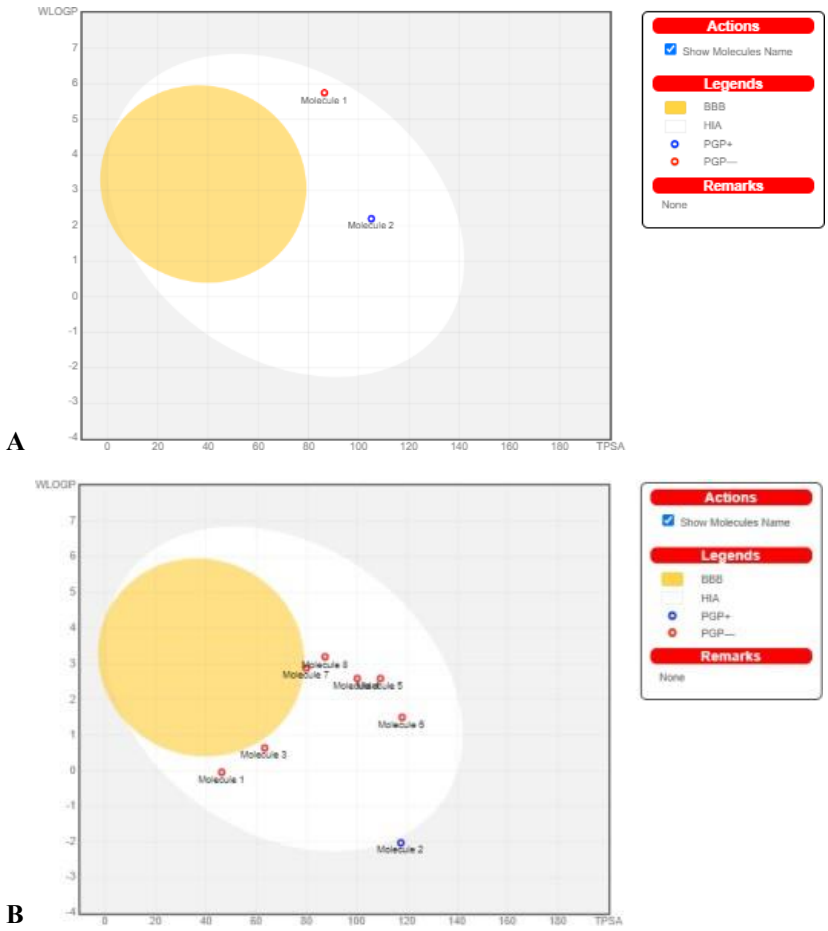

Figure 2. Location of the Screened Compound in *Boiled-Egg*
A. Native *Ligand Compound* (Comparator); B. SwissADME Passed *Metabolite Profilling* Result Compound

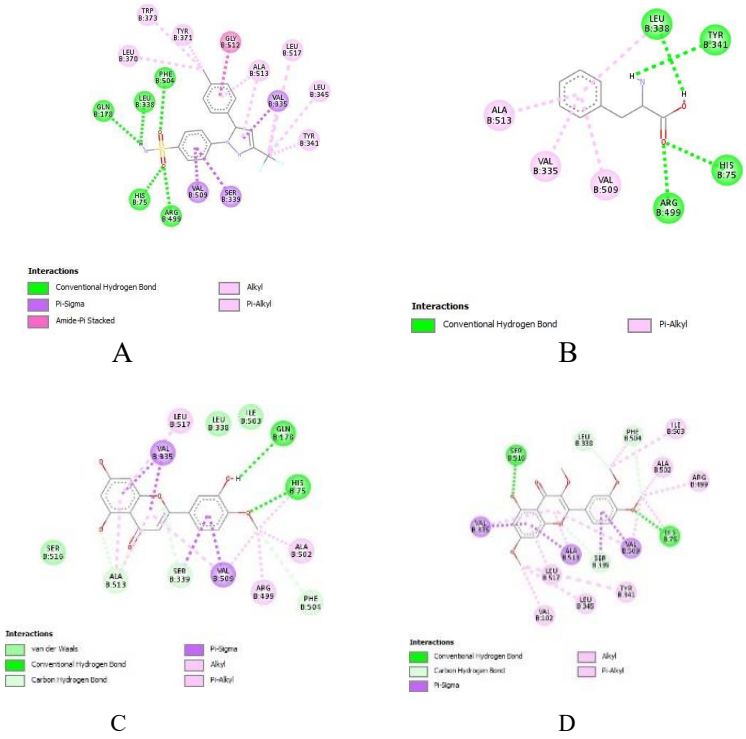

Figure 3. 2D Molecular Docking Visualization Results against 3LN1 Receptor
A. Native Ligand (Celecoxib); B. DL-Phenylalanine; C. Diosmetin; D. Retucine (Flavonol)

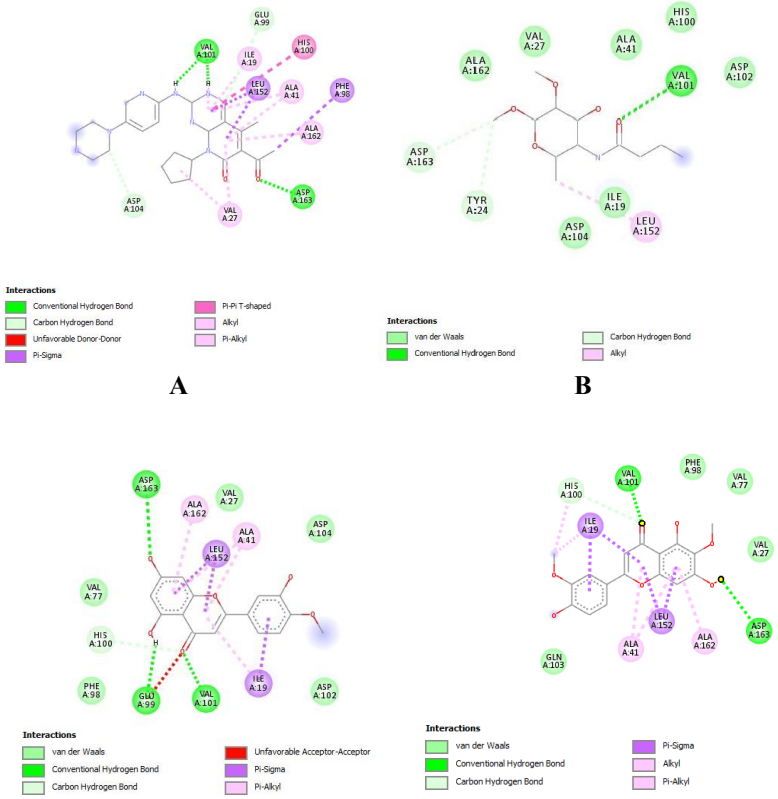

Figure 4. Visualization of Molecular Docking Results Against 5L2I Receptor
A. Native Ligand (Palbociclib); B.1,2-di-O-methyl-4-[(2R)-2,4-dihydrobutyramido]-4,6-dideoxy-α-D-mannopyranoside; C. Diosmetin; D. Jaceosine

Table 1. Prediction of Finding Compounds in Herba Chrysanthemum cinerariifolium (Trev.) Extract

Peak	Rt (min)	% Area	*Measured M/Z*	*Calculated M/Z*	Formulas	Name of Compound
1.	1,23	0,62	104,1073	104,1075	$C_5H_{13}NO$	L-(+)-Valinol
2.	1,81	0,89	294,1551	294,1553	$C_{12}H_{23}NO_7$	1,2-di-O-methyl-4-[(2R)-2,4-dihydrobutyramido]-4,6- dideoxy-α-D-mannopyranoside
3.	2,67	0,86	166,0866	166,0868	$C_9H_{11}NO_2$	DL-Phenylalanine
4.	4,37	0,60	130,1594	130,1596	$C_8H_{19}N$	Diisopropylethyl amine
5.	4,80	1,32	438,2402	438,2393	$C_{25}H_{31}N_3O_4$	Alpertine
6.	5,45	0,79	433,1334	433,1135	$C_{21}H_{20}O_{10}$	Vitexin
7.	5,80	1,03	197,1184	197,1178	$C_{11}H_{16}O_3$	1-carboxy-3-hydroxyadamantane
8.	6,33	0,38	519,1151	519,1139	$C_{24}H_{22}O_{13}$	Malonylgenistin
9.	6,93	1,00	593,1876	593,1870	$C_{28}H_{32}O_{14}$	Acaciin
10	7,34	1,24	447,1285	447,1291	$C_{22}H_{22}O_{10}$	Glycitin
11.	7,91	1,72	301,0717	301,0712	$C_{16}H_{12}O_6$	Diosmetin
12.	8,07	0,46	331,0815	331,0818	$C_{17}H_{14}O_7$	Jaceosidin
13.	8,61	0,46	229,1237	229,1229	$C_{15}H_{16}O_2$	Nabumetone
14.	9,14	3,93	345,0975	345,0974	$C_{18}H_{16}O_7$	(±)-Usnic acid
15.	9,63	7,95	285,0767	285,0763	$C_{16}H_{12}O_5$	Olmelin
16.	10,15	5,25	359,1133	359,1131	$C_{19}H_{18}O_7$	Retusin (flavonol)
17.	10,72	5,58	278,1550	278,1545	$C_{19}H_{19}NO$	1-(4-Methoxyphenyl)-N-(1-naphthylmethyl) methanamine
18.	11,15	1,73	308.1541	308,1550	$C_{16}H_{22}N_3Ocl$	Tebuconazole
19.	11,71	12,70	518,3248	518,3230	$C_{28}H_{43}N_3O_6$	N-[(trans-4-{[(N-{[(2-Methyl-2-propanyl)oxy]carbonyl}-L-leucyl)amino]me

						thyl}cyclohexyl)carbonyl]-L-phenylalanine
20.	11,83	12,70	270,1859	270,1858	$C_{18}H_{23}NO$	Orphenadrine
21.	12,05	4,41	272,2011	272,2014	$C_{18}H_{25}NO$	Dextromethorphan
22.	13,14	8,06	276,2331	276,2327	$C_{18}H_{29}NO$	TTBNB
23.	14,82	4,20	280,2642	280,2640	$C_{18}H_{33}NO$	Linoleamide
24.	15,64	7,32	593,2772	593,2764	$C_{35}H_{36}N_4O_5$	Pheophorbide A
25.	16,20	0,50	593,2773	593,2764	$C_{35}H_{36}N_4O_5$	Pheophorbide A
26.	17,45	0,70	954,6157	954, 6114	$C_7H_{62}N_{51}O_6$	Unknown
27.	17,67	0,40	1036,7710	1036,7723	$C_{52}H_{109}NO_{18}$	unknown
28.	18,41	11,01	792,5631	792,5599	$C_{41}H_{73}N_7O_8$	1,1-Dimethylethyl 4-[11-[[(2S)-5-(1,1-dimethylethoxy)-2-[4-[5- [[(1,1-dimethylethoxy)carbonyl]amino]pentyl]-1H-1,2,3-triazol-1-yl]- 1,5-dioxopentyl]amino]-1-oxoundecyl]-1-piperazinecarboxylate

Table 2. Prediction of Physiochemical Properties Using SwissADME

Name of Compound	**Parameter *Lipinski Rules of Five***				***Lipinski Rules of Five* (RoF)**	**TPSA**	***Torsion***	**Parameter HIA**		***P-GP Substrate***
	***Molecular weight* (g/mol)**	**HBA**	**HBD**	**Log P**				***GI Absorbt ion***	***BBB Permeant***	
Celecoxib*	381.37	7	7	3.40	+	86.36	6	+	-	-
Palbociclib*	447.53	6	2	2.31	+	105.04	6	+	-	+
L-(+)-Valinol	103.16	2	2	0.28	+	46.25	2	+	-	-
1,2-di-O-methyl-4-[(2R)-2,4-dihydrobutyramido]- 4,6-dideoxy-α-D-mannopyranoside	293.31	7	4	-1.08	+	117.48	7	-	-	-
DL-Phenylalanine	165.19	3	2	-0.01	+	63.32	3	+	-	-
Diosmetin	300.26	6	3	2.19	+	100.13	2	+	-	-
Jaceosidin	330.29	7	3	2.11	+	109.36	3	+	-	-
(±)-Usnic acid	344.32	7	2	1.5	+	117.97	2	+	-	-

Olmelin	284.26	5	2	2.44	+	79.9	2	+	-	-
Retusin	358.34	7	1	2.86	+	87.36	5	+	-	-

Notes:
*: Native Ligand; Molecular Weight: Molecular Weight; HBD: Hydrogen Bond Donor; HBA: Hydrogen Bond Acceptor; Log P: octanol-water partition coefficient; Lipinski Rules of Five (+): Fulfill lipinski's rules of five; Lipinski Rules of Five (-): Doesn't fulfill lipinski's rules of five; TPSA: Topological Polar Surface Area; Torsion: Number of bonds between rotatable atoms; GI Absorbtion (+): High gastrointestinal absorption; GI Absorbtion (-): Gastrointestinal absorption low; BBB Permeant (+): Can cross the blood brain barrier; BBB Permeant (-): Cannot cross the blood brain barrier; P-gp Substrate (+): Substrate to P-Glycoprotein; P-gp Substrate (–): Non-substratetoP-Glycoprotein

Table 3. Prediction of Compound Toxicity

Name of Compounds	**Toxicity**			
	Ames Toxicity	***Hepatotoxicity***	**LD_{50} (mg/kg)**	**Class**
Celecoxib*	-	+	1975	4
Palbociclib*	-	+	2778	5
L-(+)-Valinol	-	-	1946	4
1,2-di-O-methyl-4-[(2R)-2,4-dihydrobutyramido]-4,6-dideoxy-α-D-mannopyranoside	-	-	2141	5
DL-Phenylalanine	-	+	2193	5
Diosmetin	-	-	2292	5
Jaceosidine	-	-	2257	5
(±)-Usnic acid	+	+	1778	4
Olmelin	-	-	1851	4
Retucine	-	-	2416	5

Notes:
*: Native Ligand; Ames Toxicity (+): Mutagenic; Ames Toxicity (-): Non-mutagenic Hepatotoxicity (+): Causes liver damage; Hepatotoxicity (-): Does not cause liver damage.

Table 4. Molecular Docking Results of Native Ligand and Metabolite Profiling Results of Herba *Chrysanthemum cinerariifolium (Trev.)* Extracts against 3LN1 Receptor

No.	**Name of Compounds**	**Parameter *Molecular Docking***				
		***Binding Affinity* (Joule)**	***RMSD Average* (Å)**	**Interaction**	**Amino Acid (Type of Bond)**	**Pharmacophore Range**
1.	Celecoxib	-12,4	0,569	Antagonist	Leu338 (Hydrogen) Gln178 (Hydrogen) Phe504 (Hydrogen) His75 (Hydrogen) Arg499 (Hydrogen)	3,333
2.	DL-Phenylalanine	-6,3	1,014	Antagonist	Leu338 (Hydrogen) His75 (Hydrogen) Arg499	2,961

					(Hydrogen)	
3.	Diosmetin	-8,8	1,034	Antagonist	Gln178 (Hydrogen) His75 (Hydrogen) Arg499 (Alkyl) Phe504 (Carbon)	2,333
4.	Retucine (Flavonol)	-7,3	1,491	Antagonist	His75 (Hidrogen) Phe504 (Karbon) Leu338 (Karbon) Arg499 (Alkil)	4,046

Table 5. *Molecular Docking* Results of Native Ligand and *Metabolite Profiling* Results of Herba *Chrysanthemum cinerariifolium* (Trev.) Extracts against 5L2I Receptor

No.	Name of Compounds	Parameter *Molecular Docking*				
		***Binding Affinity* (Joule)**	***RMSD Average* (Å)**	**Interaction**	**Amino Acid (Type of Bond)**	**Pharmacophore Range**
1.	Palbociclib	-10,7	0,0	Antagonist	Asp163 (Hydrogen) Val101 (Hydrogen)	7,539
2.	1,2-di-O-methyl-4-[(2R)-2,4-dihydrobutyramido]- 4,6-dideoxy-α-D-mannopyranoside	-6	2,639	Antagonist	Asp163 (Hydrogen) Val101 (Hydrogen-Carbon)	7,185
3.	Diosmetin	-8,5	1,178	Antagonist	Asp163 (Hydrogen) Val101 (Hydrogen)	7,686
4.	Jaceosidine	-8,3	1,382	Antagonist	Asp163 (Hydrogen) Val101 (Hydrogen)	6,738

Conflicts of interest

No conflicts of interest among the authors in this research and publication

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