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Study of Biological Activity of the Genus Spatholobus against Breast Cancer in Silico

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Abstract: The development of apoptotic agents from natural plants has potential as promising breast cancer treatment candidates. The study on the efficacy of plants of the genus Spatholobus on breast cancer is still very limited. This study aims to explain the molecular mechanism that underlies the biological activity of breast anticancer from plants of the genus Spatholobus by in silico analysis. The method used has involved four techniques. First, the thirty-three compounds from plants of the genus Spatholobus were analyzed using the PASS server to obtain information about compounds that have breast cancer biological activity above 75%. Second, the thirteen selected compounds were evaluated using the STITCH server to determine their interactions with various proteins involved in apoptotic pathways and p53 signaling. Third, the thirteen breast anticancer compounds were re-selected to get pharmacological properties for safe consumption with the SwissADME server. Lastly, the selected nine compounds were further docked with target protein caspase-3 using the PyRx 0.99 tool and visualized with PyMol 2.5.2 and BIOVIA Discovery Studio Visualizer 2.1.1.0.2098. In conclusion, the nine compounds (lupinalbin A, trigraecum, coumestrol, maackiain, medioresinol, isoliquiritigenin, 8-O-methylretusin, biochanin A, and medicarpin) from the genus Spatholobus are predicted to have potential as activating agents for the caspase-3 protein and can suppress the growth of breast cancer cells.

Keywords: anticancer, bioactive compound, genus Spatholobus, apoptotic.

用計算機研究雞血藤屬抗乳腺癌的生物學活性

摘要：從天然植物中開發凋亡劑具有作為乳腺癌治療候選藥物的潛力。關於雞血藤屬植物對乳腺癌療效的研究仍然非常有限。本研究旨在通過計算機分析來解釋雞血藤屬植物的乳腺癌抗癌生物活性的分子機制。使用的方法涉及四種技術。首先，使用经过服務器分析了來自雞血藤屬植物的33種化合物，以獲得有關具有75%以上乳腺癌生物活性的化合物的信息。其次，使用缝服務器評估了13種選定的化合物，以確定它們與參與凋亡途徑和p53信號傳導的各種蛋白質的相互作用。第三，使用瑞士人ADME服務器重新選擇了13種乳腺癌抗癌化合物以獲得安全食用的藥理特性。最後，使用PyRx0.99工具將選定的九種化合物與目標蛋白半胱天冬酶-3 進一步對接，並使用 PyMol 2.5.2 和百奧维亚探索工作室展示台2.1.1.0.2098進行可視化。總之，來自雞血藤屬的9種化合物（羽扇豆苷一个、黄芪、香豆雌酚、麥肯、中樹脂醇、異甘草素、8鄰甲基維他命、生物鏈素A、和藥草平）預計具有作為半胱天冬酶-3蛋白激活劑的潛力並且可以抑制乳腺癌細胞的生長。

关键词：抗癌，生物活性化合物，鸡血藤属，凋亡。

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1. Introduction

The most cancer in the world in 2020 is breast cancer. WHO reports that as many as 2.26 million cases occurred, with the number of deaths 685,000 people [1]. Most anticancer agents used in clinical oncology use the intact apoptotic signaling pathway to cause cancer cell death [2]. Some proteins have been recognized to play a pivotal role in apoptotic. Caspases are a family that adjusts the process of programmed cell death [3]. Among the caspase proteins, caspase-3 activation plays an important role in suppressing the growth of breast cancer cells [4, 5]. Apoptotic is an automatic stage consisting of initiation, locution, and various genes that cause programmed cell death or remove undesired or abnormal cells in organisms and preserve a stable internal environment [6]. Defective apoptotic cancer cells grow and cause harmful mutations [7]. Apoptotic performance can be improved by natural products and supported by various experiments [8]. The natural product encompasses a major part of restorative materials in cancer treatment specifically [9]. One of the natural products with potential anticancer activity is the plant of genus Spatholobus. Some papers mentioned that the compounds from this plant could be an anticancer agents [10-12]. There are reported thirty-four species of genus Spatholobus globally, and the other five are currently being verified [13]. Based on previous reports, 33 compounds of this genus had been identified (Table 2). The publications of anti-breast cancer biological activity of compounds from genus Spatholobus plants are still limited. The initial potential activity study of genus Spatholobus compounds is urgently required. It can be carried out computationally and experimentally. The present preliminary study is conducted to predict the potential biological activity of compounds of the genus Spatholobus related to breast cancer in silico.

2. Materials and Methods

2.1. Preparation of Compound SMILES

All compound canonical SMILES of genus Spatholobus were retrieved from PubChem.

2.2. Biological Activity Analysis by PASS Server

The biological activity relates to apoptotic is at least caspase-3 stimulant, antineoplastic, apoptotic agonist, TP53 expression enhancer, caspase 8 stimulant, and anti-carcinogenic [14]. The canonical SMILES of genus Spatholobus was retrieved from PubChem and inserted in PASS server (http://way2drug.com/PassOnline/). The biological activity list will emerge along with the Pa (active) and Pi (inactive) values. This procedure set the Pa values at Pa>0.75 [15]. The score reflects the biological potential. The biological activity of the compound increased along with the high Pa score. The compounds with apoptotic related to the activity (Pa>0.75) are selected and used for further procedure.

2.3. Ligand-Protein Interaction and Network Analysis

The compounds with the highest biological activity are analyzed using STITCH server (http://stitch.embl.de/) to evaluate their interactions with proteins.

2.4. Pharmacological Properties Analysis

The properties of active compound pharmacology are scanned using the SwissADME server (http://www.swissadme.ch). The canonical SMILES of genus Spatholobus was retrieved from PubChem of most active compounds are inserted into it. The data would be listed on the server and further interpreted with the optimum criteria for safe oral consumption (molecular weight 150-500 g/mol; polarity TPSA 20-130 Å^2; solubility Log S >-6; rotatable bonds<9; lipophilicity -0.7<XLOGP3<+5.0) [16].

2.5. Molecular Docking and Visualization

This study used the nine best ligands based on the evaluation of the PASS server. The compounds were taken from PubChem and converted into PDB format using OpenBabel 3.1.1. The protein target of this research was caspase-3 (PDB ID: 1GFW) that retrieved from RSCB Protein Data Bank (https://www.rscb.org/). The protein was set to dispel water molecules and undesired ligands using PyMol 2.5.2. The selected chain was A that contained a control ligand. Molecular docking was carried out by of PyRx 0.99 (Table 6). The ligands docking to caspase-3 were managed to center x =37.078, y =33.591, and z =27.010 with dimension (Angstrom) x = 16.793, y = 14.086, and z = 38.856. The complexes of ligand-protein were presented by the PyMol tool. Biovia discovery studio visualizer 2.1.1.0.2098 was used to show the complex's active sites and 2D structures.

3. Results and Discussion

3.1. The Canonical SMILES of Genus Spatholobus Compounds

The canonical SMILES of compounds from genus Spatholobus plants are listed in Table 1. Spatholobus covers four species (S. suberectus, S. parviflorus, S. sinensis, and S. Dunn). The compounds of S. suberectus are maackiain, medicarpin, trigraecum, sativan, pseudobaptigenin, genistin [17], naringenin, protocatechuic acid ethyl ester, coumestrol, isoliquiritigenin, lupinalbin A, and leonuriside A [18]. S. parviflorus consists of medicarpin, 8-o-methylretusin, biochanin A, trans-4-hydroxymellein, cis-4-hydroxymellein, and coumestrol [19]. The compounds of S. sinensis include prestegane B, (+)-medioresinol, benzeneethanol, naringenin, blumenol A,

protocatechuic acid ethyl ester, liquiritigenin, protocatechuic acid, and glycyroside [20]. S. suberectus Dunn consists of calycosin, pyromucic acid, 1,3,5-benzenetriol, succinic acid, beta-sitosterol, suberectin [21].

3.2. Apoptotic-Related Activity Screening

The Pa value related to apoptotic is presented in Table 2. There are possibly 11 compounds with a Pa value of more than 0.75 caspase-3 stimulants. They include maackiain, medicarpin, trigraecum, genistin, medioresinol, glycyroside, beta-sitosterol, stigmasterol, isoliquiritigenin, leonuriside A, and suberectin. The predicted compounds with Pa value of antineopastic > 0.75 consist of maackiain, medicarpin, genistin, medioresinol, glycyroside, trans & cis-4-hydroxymellein, isoliquiritigenin, lupinalbin A, and leonuriside A. The estimated compounds with Pa score of apoptotic agonist higher than 0.75 covers maackiain, medicarpin, trigraecum, genistin, glycyroside, coumestrol, isoliquiritigenin, and leonuriside A.

The predicted compounds with Pa value of TP53 expression enhancer higher than 0.75 embrace medicarpin, trigraecum, genistin, medioresinol, naringenin, liquiritigenin, formononetin, daidzein, calycosin, 1,3,5-benzenetriol, biochanin A, trans & cis -4-hydroxymellein, coumestrol, lupinalbin A, leonuriside A, and suberectin. The estimated compounds with Pa value more than 0.75 of caspase-8 stimulant only include glycyroside and leonuriside A. Ultimately, the predicted compounds with Pa value higher than 0.75 cover genistin, glycyroside, and leonuriside A.

The four compounds with the highest Pa value comprise medicarpin, glycyroside, maackiain, stigmasterol, lupinalbin A, leonuriside A, medioresinol, 8-O-methylretusin, biochanin A, isoliquiritigenin, coumestrol, genistin, trigraecum, and genistin (Table 3).

3.3. Pathway Analysis and Protein Interaction

The proteins involved in the apoptotic pathway (false discovery rate 1.3x10-07) are caspase-3, Bcl2, FADD, caspase-8, TP53, and ATM. In contrast, the proteins included in the p53 signaling pathway (false discovery rate 9.31x10-10) are caspase-3, caspase-8, TP53, MDM2, ATM, CDKN1A, and CDKN2A. On pathways, isoliquiritigenin and biochanin A probably activates caspase-3 directly with percentage of 90.7% and 70.0%, respectively (Fig. 1 and Fig. 2). Caspase-3 initiates apoptotic DNA fragmentation by proteolytically inactivating DFF45/ICAD (Fig.14) and acts as a vital marker of the cell's entry point into the apoptotic signaling pathway. Caspase-3 has been revealed to cleave and activate numerous effectors, including SREBPs, caspase-6, caspase-7, and caspase-9 [22].

Table 1 SMILES of compounds from genus Spatholobus plants

No	Compound	PubChem Cid	SMILES	Ref.
1	Maackiain	91510	C1C2C(C3=C(O1)C=C(C=C3)O)OC4=CC5=C(C=C24)OCO5	[17]
2	Medicarpin	336327	COC1=CC2=C(C=C1)C3COC4=C(C3O2)C=CC(=C4)O	[17, 19]
3	Trigraecum	14376438	COC1=C(C=C2C(=C1)C(=O)C=C(O2)C3=CC=CC=C3)O	[17]
4	Sativan	596401	COC1=CC(=C(C=C1)C2CC3=C(C=C(C=C3)O)OC2)OC	[17]
5	Pseudobaptigenin	5281805	C1OC2=C(O1)C=C(C=C2)C3=COC4=C(C3=O)C=CC(=C4)O	[17]
6	Genistin	5281377	C1=CC(=CC=C1C2=COC3=CC(=CC(=C3C2=O)O)O)OC4C(C(C(C(O4)CO)O)O)O)O	[17]
7	Prestegane B	146425	COC1=C(C=C(C=C1)CC2COC(=O)C2CC3=CC(=C(C=C3)OC)O)O	[20]
8	(+)-medioresinol	181681	COC1=CC(=CC(=C1O)OC)C2C3COC(C3CO2)C4=CC(=C(C=C4)O)OC	[20]
9	Benzeneethanol	6054	C1=CC=C(C=C1)CCO	[20]
10	Naringenin	932	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O	[20, 21]
11	Blumenol A	5280462	CC1=CC(=O)CC(C1(C=CC(C)O)O)(C)C	[20]
12	Protocatechuic acid ethyl ester	77547	CCOC(=O)C1=CC(=C(C=C1)O)O	[20, 21]
13	Liquiritigenin	114829	C1C(OC2=C(C1=O)C=CC(=C2)O)C3=CC=C(C=C3)O	[20]
14	Protocatechuic acid	72	C1=CC(=C(C=C1C(=O)O)O)O	[20]
15	Glycyroside	101939210	COC1=CC=C(C=C1)C2=COC3=C(C2=O)C=CC(=C3)OC4C(C(C(C(O4)CO)O)O)O)OC5C(C(CO5)(CO)O)O	[20]
16	Formononetin	5280378	COC1=CC=C(C=C1)C2=COC3=C(C2=O)C=CC(=C3)O	[22, 19]
17	Daidzein	5281708	C1=CC(=CC=C1C2=COC3=C(C2=O)C=CC(=C3)O)O	[22,[19]
18	Calycosin	5280448	COC1=C(C=C(C=C1)C2=COC3=C(C2=O)C=CC(=C3)O)O	[22]
19	Pyromucic acid	6919	C1=COC(=C1)C(=O)O	[22]
20	1,3,5-benzenetriol	359	C1=C(C=C(C=C1O)O)O	[22]
21	Succinic acid	1110	C(CC(=O)O)C(=O)O	[22]
22	Beta-sitosterol	222284	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C	[22]
23	Stigmasterol	5280794	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C	[19]
24	(6aR,11aR)-medicarpin	336327	COC1=CC2=C(C=C1)C3COC4=C(C3O2)C=CC(=C4)O	
25	8-O-methylretusin	5319771	COC1=CC=C(C=C1)C2=COC3=C(C2=O)C=CC(=C3OC)O	[19]
26	Biochanin A	5280373	COC1=CC=C(C=C1)C2=COC3=CC(=CC(=C3C2=O)O)O	[19]

Continuation of Table 1

27	Trans-4-Hydroxymellein	10262028	CC1C(C2=C(C(=CC=C2)O)C(=O)O1)O	[19]
28	Cis-4-Hydroxymellein	10420140	CC1C(C2=C(C(=CC=C2)O)C(=O)O1)O	[19]
29	Coumestrol	5281707	C1=CC2=C(C=C1O)OC3=C2C(=O)OC4=C3C=CC(=C4)O	[19, 21]
30	Isoliquiritigenin	638278	C1=CC(=CC=C1C=CC(=O)C2=C(C=C(C=C2)O)O)O	[21]
31	Lupinalbin A	5324349	C1=CC2=C(C=C1O)OC3=C2C(=O)C4=C(C=C(C=C4O3)O)O	[21]
32	Leonuriside A	14237625	COC1=CC(=CC(=C1OC2C(C(C(C(O2)CO)O)O)O)O)OC)O	[21]
33	Suberectin	5321538	COC1=C(O)C=C2OC(CC(=O)C2=C1)C1=CC(O)=C(O)C=C1	[22]

Table 2 Apoptotic-related activity screening results

No	Compounds	Pa > 0.75					
		Caspase-3 stimulant	Antineoplastic	Apoptotic agonist	TP53 expression enhancer	Caspase-8 stimulant	Anti-carcinogenic
1	Maackiain	0.934	0.788	0.751	-	-	-
2	Medicarpin	0.991	0.769	0.778	0.774	-	-
3	Trigraecum	0.751	-	0.769	0.863	-	-
4	Sativan	-	-	-	-	-	-
5	Pseudobaptigenin	-	-	-	-	-	-
6	Genistin	0.763	0.814	0.757	0.912	-	0.951
7	Prestegane B	-	-	-	-	-	-
8	(+)-medioresinol	0.757	0.812	-	0.800	-	-
9	Benzeneethanol	-	-	-	-	-	-
10	4,7,2'-trihydroxy-4'-methoxyisoflavone	-	-	-	-	-	-
11	Naringenin	-	-	-	0.822	-	-
12	Blumenol A	-	-	-	-	-	-
13	Protocatechuic acid ethyl ester	-	-	-	-	-	-
14	Liquiritigenin	-	-	-	0.769	-	-
15	protocatechuic acid	-	-	-	-	-	-
16	Glycyroside	0.975	0.864	0.790	-	0.857	0.922
17	Formononetin	-	-	-	0.770	-	-
18	Daidzein	-	-	0.755	0.771	-	-
19	Calycosin	-	-	0.779	0.797	-	-
20	Pyromucic acid	-	-	-	-	-	-
21	1,3,5-benzenetriol	-	-	-	0.752	-	-
22	Succinic acid	-	-	-	-	-	-
23	Beta-sitosterol	0.806	-	-	-	-	-
24	Stigmasterol	0.863	-	0.753	-	-	-
25	8-O-methylretusin	-	-	0.827	-	-	-
26	Biochanin A	-	-	0.823	0.823	-	-
27	Trans-4-Hydroxymellein	-	0.790	-	0.796	-	-
28	Cis-4-Hydroxymellein	-	0.790	-	0.796	-	-
29	Coumestrol	-	-	0.811	0.769	-	-
30	Isoliquiritigenin	0.793	0.752	0.812	-	-	-
31	lupinalbin A	-	0.953	-	0.789	-	-
32	Leonuriside A	0.862	0.829	0.712	0.835	0.762	0.833
33	Suberectin	0.751	-	-	0.780	-	-

Table 3 Four highest Pa value (>0.75) related to apoptotic

Biological activity	Four highest Pa value
Caspase-3 stimulant	Medicarpin (0.991), glycyroside (0.975), maackiain (0.934), Stigmasterol (0.863)
Antineoplastic	lupinalbin A (0.953), glycyroside (0.864), leonuriside A (0.829), medioresinol (0.812)
Apoptotic agonist	8-O-methylretusin (0.827), biochanin A (0.823), isoliquiritigenin (0.812), coumestrol (0.811)
TP53 expression enhancer	genistin (0.911), trigraecum (0.863), leonuriside A (0.835), biochanin A (0.823)
Caspase 8 stimulant	glycyroside (0.857), leonuriside A (0.762)
Anticarcinogenic	genistin (0.951), glycyroside (0.922), Leonuriside A(0.833)

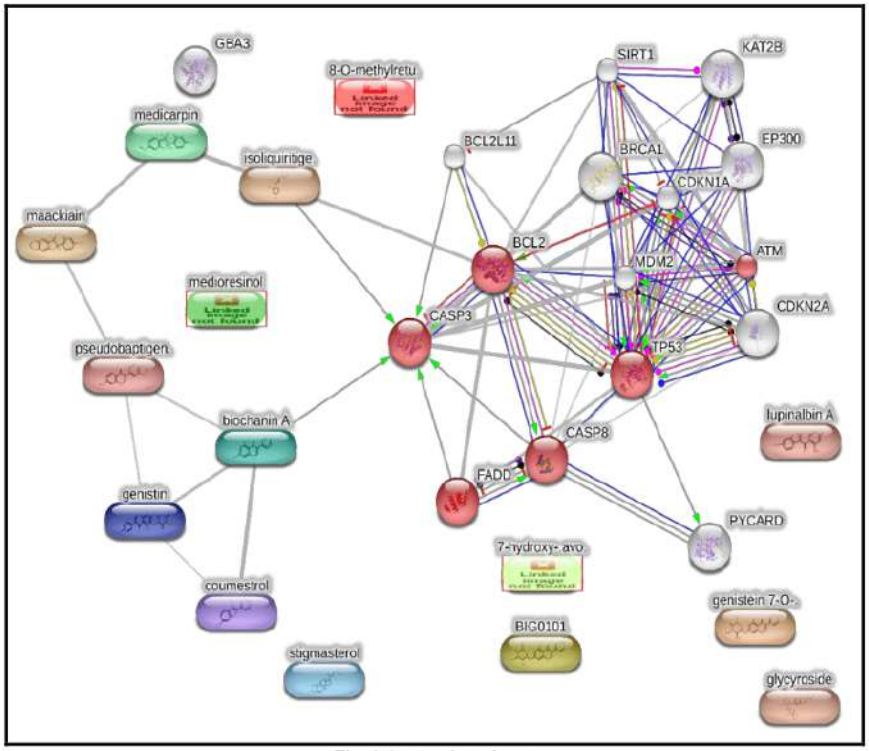


Fig. 1 Apoptotic pathway

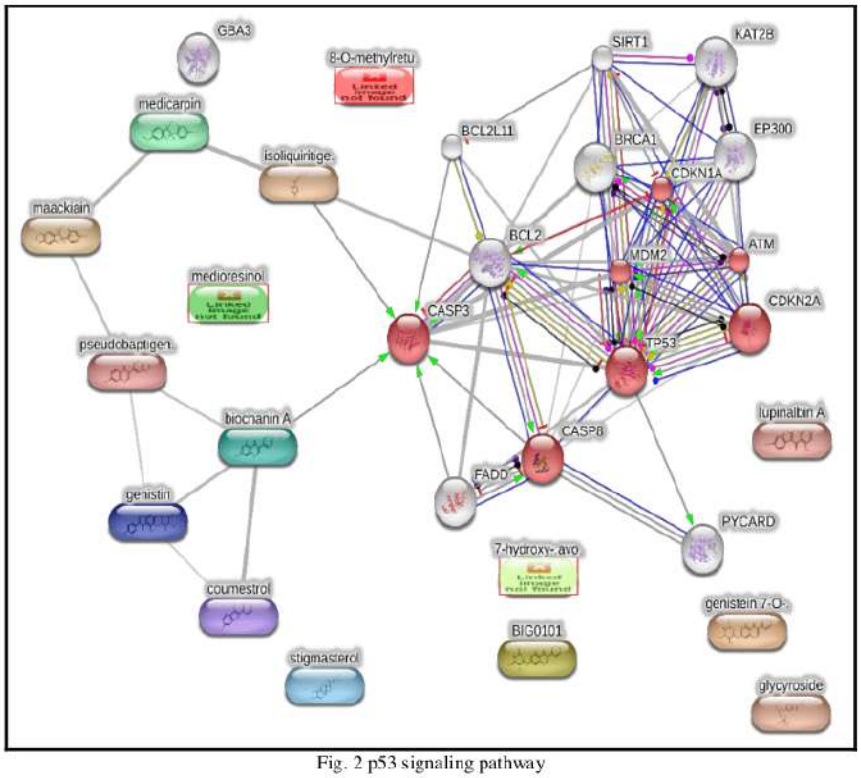


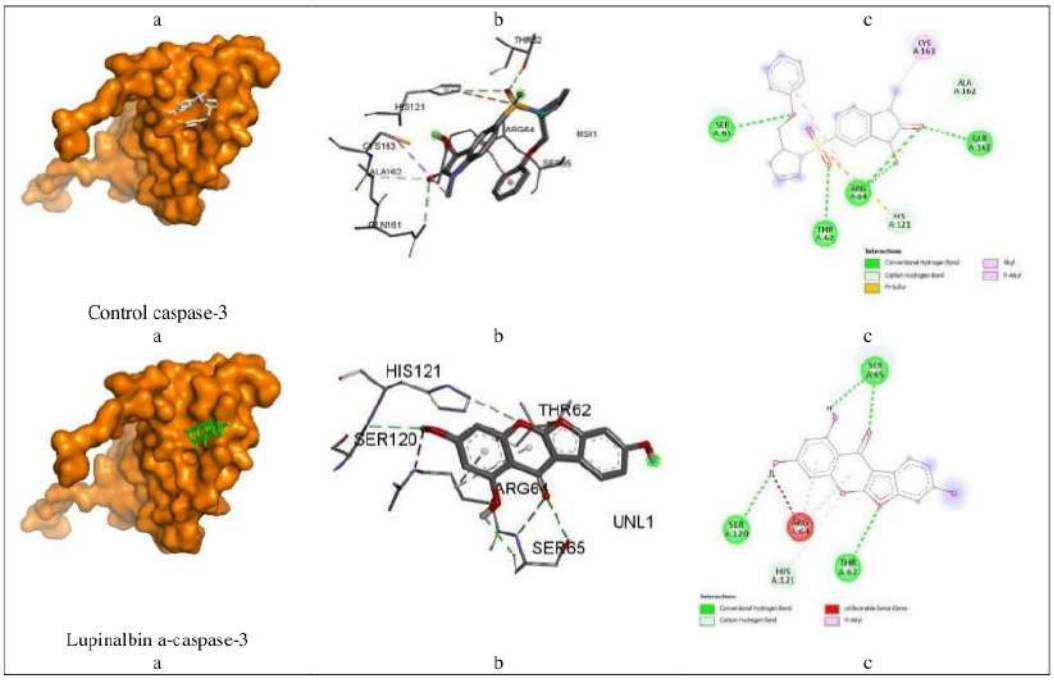
Fig. 2 p53 signaling pathway

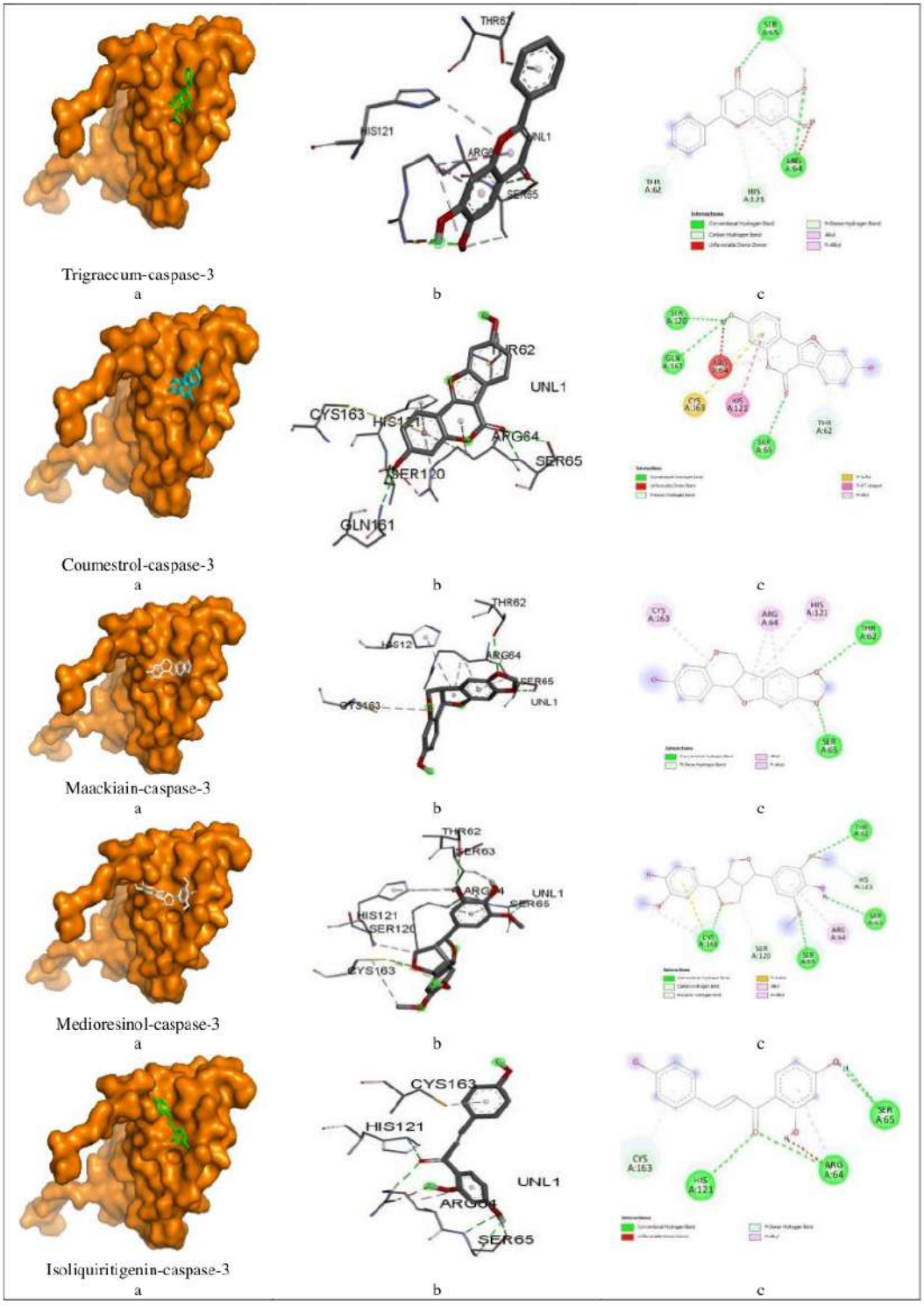
Table 4 Results of the analysis of pharmacological properties

No	Compound	Molecular weight (g/mol)	LogP values	Solubility (Log S)	Flexibility			Lipophilicity (Log P)
					H-bond acceptors	H-bond donors	Rotatable bonds	
1	Medicarpin	270.28	47.92 Å²	-3.64	4	1	1	2.77
2	Glycyroside	562.52	197.74 Å²	-2.95	13	6	8	-0.23
3	Maackiain	284.26	57.15 Å²	-3.67	5	1	0	2.61
4	Stigmasterol	412.69	20.23 Å²	-7.46	1	1	5	8.56
5	Lupinalbin A	284.22	104.04 Å²	-4.2	6	3	0	3.18
6	Leonuriside A	332.3	138.07 Å²	-1.2	9	5	5	-0.90
7	Medioresinol	388.41	86.61 Å²	-3.65	7	2	5	2.25
8	8-O-methylretusin	298.29	68.90 Å²	-3.77	5	1	3	2.77
9	Biochanin A	284.26	79.90 Å²	-3.92	5	2	2	2.99
10	Isoliquiritigenin	256.25	77.76 Å²	-3.7	4	3	3	3.18
11	Coumestrol	268.22	83.81 Å²	-3.87	5	2	0	2.76
12	Genistin	432.38	170.05 Å²	-3.18	10	6	4	0.86
13	Trigraecum	268.26	59.67 Å²	-4.22	4	1	2	3.59

Table 5 Binding affinity of nine chosen compounds of genus Spatholobus

Compounds	Binding affinity (kcal/mol)
	Caspase-3
1-methyl-5-(2-phenoxymethyl-pyrrolidine-1-sulfonyl)-1h-indole-2,3-dione (MSI/control)	-5.4
Lupinalbin A	-5.5
Trigraecum	-5.5
Coumestrol	-5.3
Maackiain	-5.2
Medioresinol	-5.2
Isoliquiritigenin	-5.0
8-O-methylretusin	-4.9
Biochanin A	-4.9
Medicarpin	-4.7

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HIS121
UNL1
ARG64
SER65
Trigraecum-caspase-3
a
b
c
CYS163
HIS121
SER120
GLN161
Coumestrol-caspase-3
a
b
c
Maackiain-caspase-3
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c
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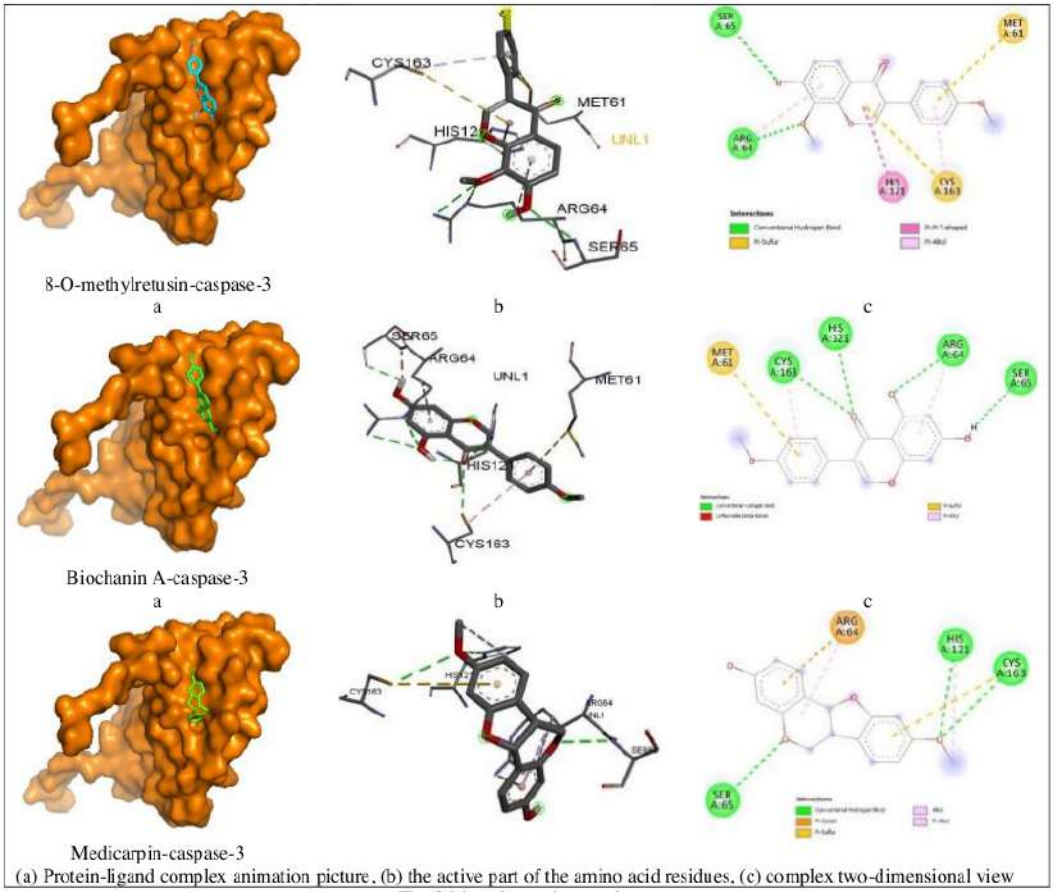
b
c
Isoliquiritigenin-caspase-3
a
b
c



(a) Protein-ligand complex animation picture, (b) the active part of the amino acid residues, (c) complex two-dimensional view

Fig. 3 Ligand-protein complexes

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:THR62:OG1 - A:MSI1:O4	☑ Yes		Ligand Non-bond Monitor	2.87578	Hydrogen Bond	Conventional Hydrogen Bond
2	A:ARG64:NE - A:MSI1:O3	☑ Yes		Ligand Non-bond Monitor	2.95204	Hydrogen Bond	Conventional Hydrogen Bond
3	A:ARG64:NH2 - A:MSI1:O2	☑ Yes		Ligand Non-bond Monitor	3.1977	Hydrogen Bond	Conventional Hydrogen Bond
4	A:SER65:N - A:MSI1:O1	☑ Yes		Ligand Non-bond Monitor	3.02727	Hydrogen Bond	Conventional Hydrogen Bond
5	A:GLN161:NE2 - A:MSI1:O2	☑ Yes		Ligand Non-bond Monitor	3.02539	Hydrogen Bond	Conventional Hydrogen Bond
6	A:HIS121:CE1 - A:MSI1:O4	☑ Yes		Ligand Non-bond Monitor	3.44982	Hydrogen Bond	Carbon Hydrogen Bond
7	A:ALA162:CA - A:MSI1:O2	☑ Yes		Ligand Non-bond Monitor	3.60093	Hydrogen Bond	Carbon Hydrogen Bond
8	A:MSI1:S1 - A:HIS121	☑ Yes		Ligand Non-bond Monitor	5.58769	Other	Pi-Sulfur
9	A:MSI1 - A:MSI1	☑ Yes		Ligand Non-bond Monitor	3.87583	Hydrophobic	Pi-Pi Stacked
10	A:MSI1:C1 - A:CYS163	☑ Yes		Ligand Non-bond Monitor	4.91414	Hydrophobic	Alkyl
11	A:MSI1 - A:ARG64	☑ Yes		Ligand Non-bond Monitor	5.4687	Hydrophobic	Pi-Alkyl

Fig. 4 MSI-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:THR62:OG1 - :UNL1:O	☑ Yes		Ligand Non-bond Monitor	2.84391	Hydrogen Bond	Conventional Hydrogen Bond
2	A:SER65:N - :UNL1:O	☑ Yes		Ligand Non-bond Monitor	3.14708	Hydrogen Bond	Conventional Hydrogen Bond
3	A:SER65:OG - :UNL1:O	☑ Yes		Ligand Non-bond Monitor	2.84356	Hydrogen Bond	Conventional Hydrogen Bond
4	:UNL1:H - A:SER65:O	☑ Yes		Ligand Non-bond Monitor	2.40886	Hydrogen Bond	Conventional Hydrogen Bond
5	:UNL1:H - A:SER120:O	☑ Yes		Ligand Non-bond Monitor	2.89309	Hydrogen Bond	Conventional Hydrogen Bond
6	A:HIS121:CE1 - :UNL1:O	☑ Yes		Ligand Non-bond Monitor	3.63639	Hydrogen Bond	Carbon Hydrogen Bond
7	:UNL1 - A:ARG64	☑ Yes		Ligand Non-bond Monitor	4.5798	Hydrophobic	Pi-Alkyl
8	:UNL1 - A:ARG64	☑ Yes		Ligand Non-bond Monitor	3.80441	Hydrophobic	Pi-Alkyl

Fig. 5 Lupinalbin A-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:ARG64:NH2 - :UNL1:O	Yes		Ligand Non-bond Monitor	2.98432	Hydrogen Bond	Conventional Hydrogen Bond
2	A:SER65:N - :UNL1:O	Yes		Ligand Non-bond Monitor	3.07322	Hydrogen Bond	Conventional Hydrogen Bond
3	A:SER65:OG - :UNL1:O	Yes		Ligand Non-bond Monitor	2.83035	Hydrogen Bond	Conventional Hydrogen Bond
4	A:HIS121:CE1 - :UNL1:O	Yes		Ligand Non-bond Monitor	3.65641	Hydrogen Bond	Carbon Hydrogen Bond
5	:UNL1:C - A:SER65:O	Yes		Ligand Non-bond Monitor	3.28245	Hydrogen Bond	Carbon Hydrogen Bond
6	A:THR62:OG1 - :UNL1	Yes		Ligand Non-bond Monitor	3.40677	Hydrogen Bond	Pi-Donor Hydrogen Bond
7	:UNL1:C - A:ARG64	Yes		Ligand Non-bond Monitor	4.2964	Hydrophobic	Alkyl
8	:UNL1 - A:ARG64	Yes		Ligand Non-bond Monitor	4.71568	Hydrophobic	Pi-Alkyl
9	:UNL1 - A:ARG64	Yes		Ligand Non-bond Monitor	3.88577	Hydrophobic	Pi-Alkyl

Fig. 6 Trigraecum-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:SER65:...	Yes		Ligand Non-bond Monitor	2.95405	Hydrogen Bond	Conventional Hydrogen Bond
2	A:SER65:...	Yes		Ligand Non-bond Monitor	3.03504	Hydrogen Bond	Conventional Hydrogen Bond
3	A:GLN16...	Yes		Ligand Non-bond Monitor	3.22306	Hydrogen Bond	Conventional Hydrogen Bond
4	:UNL1:H -...	Yes		Ligand Non-bond Monitor	2.40531	Hydrogen Bond	Conventional Hydrogen Bond
5	A:THR62:...	Yes		Ligand Non-bond Monitor	3.32003	Hydrogen Bond	Pi-Donor Hydrogen Bond
6	A:ARG64...	Yes		Ligand Non-bond Monitor	3.99645	Hydrogen Bond	Pi-Donor Hydrogen Bond
7	A:CYS16...	Yes		Ligand Non-bond Monitor	5.13825	Other	Pi-Sulfur
8	A:HIS121...	Yes		Ligand Non-bond Monitor	4.86047	Hydrophobic	Pi-Pi T-shaped
9	:UNL1 - A...	Yes		Ligand Non-bond Monitor	4.2775	Hydrophobic	Pi-Alkyl
10	:UNL1 - A...	Yes		Ligand Non-bond Monitor	4.6308	Hydrophobic	Pi-Alkyl

Fig. 7 Coumestrol-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:THR62:OG1 - :UNL1:O	Yes		Ligand Non-bond Monitor	3.02672	Hydrogen Bond	Conventional Hydrogen Bond
2	A:SER65:OG - :UNL1:O	Yes		Ligand Non-bond Monitor	2.99719	Hydrogen Bond	Conventional Hydrogen Bond
3	A:SER65:N - :UNL1	Yes		Ligand Non-bond Monitor	4.15684	Hydrogen Bond	Pi-Donor Hydrogen Bond
4	A:ARG64 - :UNL1	Yes		Ligand Non-bond Monitor	3.84283	Hydrophobic	Alkyl
5	A:CYS163 - :UNL1	Yes		Ligand Non-bond Monitor	5.35575	Hydrophobic	Alkyl
6	A:HIS121 - :UNL1	Yes		Ligand Non-bond Monitor	5.28664	Hydrophobic	Pi-Alkyl
7	:UNL1 - A:ARG64	Yes		Ligand Non-bond Monitor	4.19047	Hydrophobic	Pi-Alkyl

Fig. 8 Maackiain-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:THR62:OG1 - :UNL1:O	Yes		Ligand Non-bond Monitor	2.83267	Hydrogen Bond	Conventional Hydrogen Bond
2	A:SER65:OG - :UNL1:O	Yes		Ligand Non-bond Monitor	2.70235	Hydrogen Bond	Conventional Hydrogen Bond
3	A:CYS163:SG - :UNL1:O	Yes		Ligand Non-bond Monitor	3.64806	Hydrogen Bond	Conventional Hydrogen Bond
4	:UNL1:H - A:SER63:O	Yes		Ligand Non-bond Monitor	2.46442	Hydrogen Bond	Conventional Hydrogen Bond
5	A:HIS121:CE1 - :UNL1:O	Yes		Ligand Non-bond Monitor	3.41152	Hydrogen Bond	Carbon Hydrogen Bond
6	:UNL1:C - A:SER120:O	Yes		Ligand Non-bond Monitor	3.74833	Hydrogen Bond	Carbon Hydrogen Bond
7	A:SER65:N - :UNL1	Yes		Ligand Non-bond Monitor	4.1737	Hydrogen Bond	Pi-Donor Hydrogen Bond
8	A:CYS163:SG - :UNL1	Yes		Ligand Non-bond Monitor	3.90601	Other	Pi-Sulfur
9	:UNL1:C - A:CYS163	Yes		Ligand Non-bond Monitor	4.40746	Hydrophobic	Alkyl
10	A:HIS121 - :UNL1:C	Yes		Ligand Non-bond Monitor	4.86624	Hydrophobic	Pi-Alkyl
11	:UNL1 - A:ARG64	Yes		Ligand Non-bond Monitor	4.03388	Hydrophobic	Pi-Alkyl

Fig. 9 Medioresinol-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:ARG64:NE - :UNL1:O	Yes		Ligand Non-bond Monitor	2.93039	Hydrogen Bond	Conventional Hydrogen Bond
2	A:SER65:N - :UNL1:O	Yes		Ligand Non-bond Monitor	2.90309	Hydrogen Bond	Conventional Hydrogen Bond
3	A:SER65:OG - :UNL1:O	Yes		Ligand Non-bond Monitor	2.93161	Hydrogen Bond	Conventional Hydrogen Bond
4	A:HIS121:ND1 - :UNL1:O	Yes		Ligand Non-bond Monitor	3.14281	Hydrogen Bond	Conventional Hydrogen Bond
5	:UNL1:H - A:SER65:O	Yes		Ligand Non-bond Monitor	2.21606	Hydrogen Bond	Conventional Hydrogen Bond
6	A:CYS163:SG - :UNL1	Yes		Ligand Non-bond Monitor	3.79127	Hydrogen Bond;Other	Pi-Donor Hydrogen Bond;Pi-Sulfur
7	:UNL1 - A:ARG64	Yes		Ligand Non-bond Monitor	3.95478	Hydrophobic	Pi-Alkyl

Fig. 10 Isoliquiritigenin-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:ARG64...	Yes		Ligand Non-bond Monitor	3.29203	Hydrogen Bond	Conventional Hydrogen Bond
2	A:ARG64...	Yes		Ligand Non-bond Monitor	3.13906	Hydrogen Bond	Conventional Hydrogen Bond
3	A:SER65:...	Yes		Ligand Non-bond Monitor	3.16316	Hydrogen Bond	Conventional Hydrogen Bond
4	A:MET61:...	Yes		Ligand Non-bond Monitor	5.22337	Other	Pi-Sulfur
5	A:CYS16...	Yes		Ligand Non-bond Monitor	5.00118	Other	Pi-Sulfur
6	A:HIS121...	Yes		Ligand Non-bond Monitor	4.51993	Hydrophobic	Pi-Pi T-shaped
7	:UNL1 - A...	Yes		Ligand Non-bond Monitor	4.27625	Hydrophobic	Pi-Alkyl
8	:UNL1 - A...	Yes		Ligand Non-bond Monitor	4.99271	Hydrophobic	Pi-Alkyl

Fig. 11 8-O-methylretusin-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:ARG64:NE - :UNL1:O	Yes		Ligand Non-bond Monitor	3.11202	Hydrogen Bond	Conventional Hydrogen Bond
2	A:ARG64:NH2 - :UNL1:O	Yes		Ligand Non-bond Monitor	3.38887	Hydrogen Bond	Conventional Hydrogen Bond
3	A:HIS121:ND1 - :UNL1:O	Yes		Ligand Non-bond Monitor	3.12312	Hydrogen Bond	Conventional Hydrogen Bond
4	A:CYS163:SG - :UNL1:O	Yes		Ligand Non-bond Monitor	3.51055	Hydrogen Bond	Conventional Hydrogen Bond
5	:UNL1:H - :UNL1:O	Yes		Ligand Non-bond Monitor	1.7913	Hydrogen Bond	Conventional Hydrogen Bond
6	:UNL1:H - A:SER65:O	Yes		Ligand Non-bond Monitor	2.42998	Hydrogen Bond	Conventional Hydrogen Bond
7	A:MET61:SD - :UNL1	Yes		Ligand Non-bond Monitor	5.08124	Other	Pi-Sulfur
8	:UNL1 - A:ARG64	Yes		Ligand Non-bond Monitor	4.14095	Hydrophobic	Pi-Alkyl
9	:UNL1 - A:CYS163	Yes		Ligand Non-bond Monitor	5.01979	Hydrophobic	Pi-Alkyl

Fig. 12 Biochanin A-caspase-3 interactions

	Name	Visible	Color	Parent	Distance	Category	Types
1	A:SER65:N - :UNL1:O	Yes		Ligand Non-bond Monitor	3.28962	Hydrogen Bond	Conventional Hydrogen Bond
2	A:HIS121:ND1 - :UNL1:O	Yes		Ligand Non-bond Monitor	3.35119	Hydrogen Bond	Conventional Hydrogen Bond
3	A:CYS163:SG - :UNL1:O	Yes		Ligand Non-bond Monitor	3.69895	Hydrogen Bond	Conventional Hydrogen Bond
4	A:ARG64:NH2 - :UNL1	Yes		Ligand Non-bond Monitor	3.79389	Electrostatic	Pi-Cation
5	A:CYS163:SG - :UNL1	Yes		Ligand Non-bond Monitor	5.34761	Other	Pi-Sulfur
6	A:ARG64 - :UNL1	Yes		Ligand Non-bond Monitor	4.92458	Hydrophobic	Alkyl
7	A:HIS121 - :UNL1:C	Yes		Ligand Non-bond Monitor	4.67437	Hydrophobic	Pi-Alkyl
8	:UNL1 - A:ARG64	Yes		Ligand Non-bond Monitor	5.27431	Hydrophobic	Pi-Alkyl

Fig. 13 Medicarpin-caspase-3 interactions

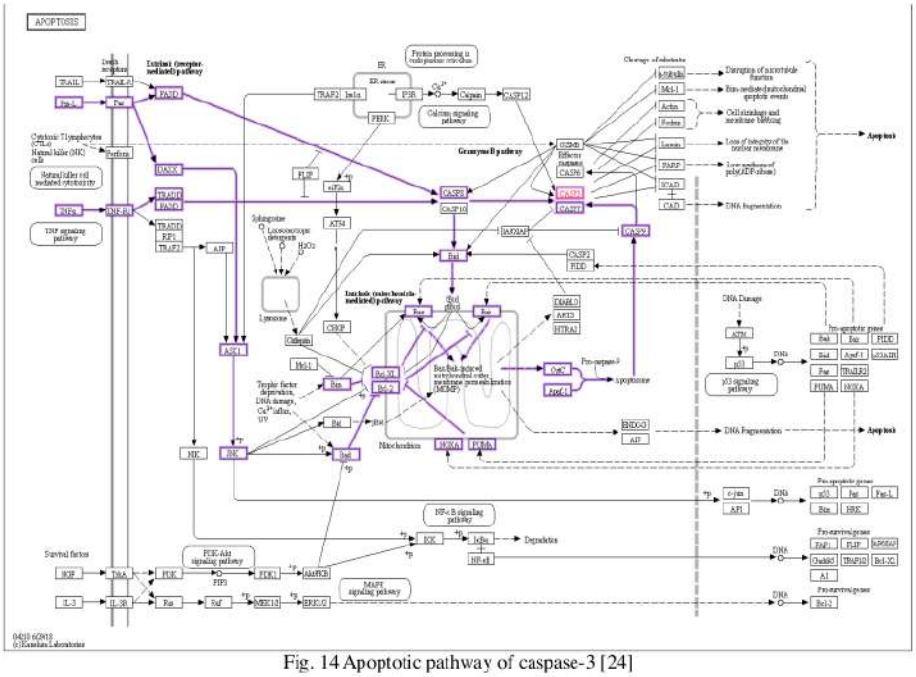


Fig. 14 Apoptotic pathway of caspase-3 [24]

In addition, according to the apoptotic pathway, isoliquiritinigen interacts with Bcl2 directly (70.0%), but there is no explanation about the interaction type. Meanwhile, the other ligands show no interaction with proteins on both pathways. We assume that the database of STITCH is not updated yet, or the latest report is unavailable.

3.4. SwissADME Analysis

The list of pharmacological properties of active compounds is presented in Table 4. Based on the optimum criteria, glycyroside (MW>500 g, TPSA>130 Å²), stigmasterol (Log S< -6, Log P3>5), leonuriside A (TPSA>130 Å²), and genistin (TPSA>130 Å²) do not meet the optimum criteria of pharmacological properties. In contrast, the others are under the appropriate criteria.

3.5. Molecular Docking Analysis

The caspase-3 protein (PDB ID 1GFW) has active sites on HIS 121 and Cyst (cysteine) 163 in A Chain. The active site of this protein is indicated by the type of interaction between protein and ligand acetamide derivative. These interactions occur in the A chain; the types of interaction are Pi-sulfur cystine 163, Pi-Pi T-shaped HIS 121, and pi-cation HIS 121 [23]. Docking results also show that natural ligands or compounds interact with the active site of amino acid residues.

Control ligand (MSI) interacts with HIS 121 (carbon-hydrogen bond and pi-sulfur) and Cys 163 (alkyl). Lupinalbin A interacts with HIS 121 (carbon-hydrogen bond), trigraecum – with HIS121 (carbon-hydrogen bond), coumestrol – with Cys163 (pi-sulfur) and HIS 121 (Pi-Pi T-shaped), maackiain – with Cys 163 (alkyl), and HIS 121 (Pi-Alkyl). Medioresinol interacts with Cyst 163 and HIS 121 in conventional hydrogen, carbon-hydrogen, and pi alkyl bonds. Isoliquiritigenin links HIS 121 and Cys 163 through conventional hydrogen, pi-donor hydrogen, and pi-sulfur bonds. At the same time, 8-o-methylretusin interacts with Cys 163 (Pi-Sulfur) and HIS 121 (Pi-Pi T-shaped). Biochanin interacts with HIS 121 (Conventional Hydrogen Bond) and Cys 163 (Conventional Hydrogen Bond), medicarpin – with HIS 121 (Conventional Hydrogen Bond), Cys 163 (Conventional Hydrogen Bond), and HIS 121 (Pi-Alkyl) (Figs. 4-13).

Overall, all ligands interact with the active site of the protein caspase-3. However, other amino acid residues apart from HIS 121 and Cys 136 interact with natural ligands. The molecular docking analysis shows that the highest binding affinity against caspase-3 is found in the lupinalbin A and trigacum (-5.5 kcal/mol). Meanwhile, other ligands have binding affinity under their control ligands (Table 5). Thus, both lupinalbin A and trigacum compounds have the highest potential as caspase-3 activator agents and suppress breast cancer cell growth.

Caspase-3 protein (PDB ID 1GFW) was also used as a target model in molecular docking studies with compounds from Moringa oleifera fruit. The results show that these compounds have anticancer activity, and there is a match between the molecular docking simulation test and the in vitro test [24].

4. Conclusion

Based on the analysis results of various procedures, caspase-3 is probably as target protein in the apoptotic and p53 signaling pathways. Due to software limitations, the presence of water molecules in the molecular docking was intentionally ignored. So in further study, this needs to be validated with dynamic molecular simulations. In addition, in vitro study of apoptotic cancer cell models is also required to support the provisional hypothesis that caspase-3 can be activated by bioactive compounds from plants of the genus Spatholobus. Furthermore, the estimated nine compounds that meet the optimum criteria to be consumed orally are medicarpin, maackiain, lupinalbin A, medioresinol, 8-O-methylretusin, biochanin A, isoliquiritigenin, coumestrol, and trigraecum. These compounds are probably nominated as protein activators of caspase-3 in both pathways.

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