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MOLECULAR DOCKING ANALYSIS OF SESQUITERPENES WITH ANTI-APOPTOTIC PROTEIN (BCL-2 AND BCL-XL) AND PREDICTING THEIR PHYSICOCHEMICAL PROPERTIES

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Cancer, Sesquiterpene lactones, Apoptosis, Bcl-2 family, Molecular docking

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ABSTRACT: One of the main causes of mortality around the globe is cancer. Cell division routes increase as cancer progresses, but planned cell death decreases. As a result, cancer is characterized by a variety of these failing systems. The present study used an *in-silico* approach to examine the ability of sesquiterpene lactones to inhibit the anti-apoptotic proteins Bcl-2 and Bcl-xl. Numerous Bcl-2 inhibitors are undergoing clinical studies. Using PyRx AutodockVina, the phytocompounds were further examined for their *in-silico* docking interactions. It is interesting to develop novel Bcl-2 inhibitors from phytocompounds such as Arctigenin, Arteminolide C, Gaillardin, Helenalin, and Ixerin D, which have binding affinity scores similar to obatoclax. Potential binding mechanisms within the receptor's active sites were explored using molecular docking studies of all active substances into the binding sites of Bcl-2 and Bcl-xl, and the physiochemical properties of the phytocompounds were predicted according to Lipinski's rule of five.

INTRODUCTION: Cancer is one of the leading causes of mortality worldwide. In 2018, there were 18.1 million new cases of cancer and 9.5 million cancer-related deaths. By 2040, there will be 29.5 million new instances of cancer yearly, according to predictions. The highest prevalence of cancer is often seen in countries with high standards of living and lengthy life expectancies [1]. The protracted process of cell division and cell death is tightly controlled in multicellular organisms. Dysregulation of one of these biological processes affects the normal development and homeostasis that result in cancer.

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Cell proliferation pathways are increased as cancer progresses, whereas planned cell death or apoptotic pathways are decreased. As a result, the repertory of these failing systems is a characteristic of cancer [2]. Anti-cancer therapies exert their harmful effects by inducing apoptosis, or regulating cell death. Apoptosis, which is linked to both carcinogenesis and anticancer medication resistance, is commonly avoided by cancer cells.

By inhibiting cell turnover brought on by natural cell death processes rather than speeding up rates of cell division, Bcl-2, a blocker of planned cell death and apoptosis, aids in the growth of malignant cells [2]. Cancer cells abundantly produce anti-apoptotic proteins, helping them survive by inhibiting apoptosis. Anti-apoptotic proteins are now a sought-after target for the development of cancer treatments. IAPs (Inhibitor of Apoptosis) proteins and the Bcl-2 (B-cell lymphoma-2) family of proteins are the two main anti-apoptotic protein

families [3, 4]. Changes in the Bcl-2 family of proteins, crucial apoptosis regulators, cause B cell lymphoma. Over the past 30 years, significant efforts have been made to increase our understanding of biology, molecular processes, and the therapeutic potential of targeting Bcl-2 family members [5]. The process of apoptosis is crucial for maintaining tissue and embryonic homeostasis. Apoptosis consists of the three main stages of initiation, commitment, and execution. The two separate groups of apoptosis proteins include proapoptotic proteins (Bax and Bak) and anti-apoptotic proteins (Bcl-2, Bcl-xL, Bcl-W and Mcl-1). The release of cytochrome C and subsequent activation of caspases during the induction of apoptosis by mitochondrial outer membrane permeability depends on pro-apoptotic proteins. Due to the excess of anti-apoptotic proteins that can impede apoptosis by building heterodimers with pro-apoptotic proteins and subsequently inactivating them, the ratio of anti-apoptotic to pro-apoptotic proteins, which is normally balanced, is out of balance in cancer. Finding substances that promote apoptosis by focusing on both intrinsic and extrinsic apoptotic pathways by understanding the mechanism underlying tumor cell proliferation might lead to the creation of effective cancer treatments [2, 6].

Current cancer treatment options include surgery and radiation therapy for the extensive accumulated cancer biomass, usually followed by systemic chemotherapy for maintenance. The main drawbacks of chemotherapy include cancer recurrence, drug resistance, and harmful effects on organs that aren't being targeted, which can limit the use of anticancer medications and reduce the quality of life for patients. Plant-based phytochemicals and their derivatives promise to increase cancer patients' response rates and reduce side effects. Several of these phytochemicals are biologically active substances that are present in nature and have substantial anticancer properties. The development of effective and side-effects free phytochemical-based anticancer therapy [7]. Phytochemicals have become more well-known recently because they can change metastasis, angiogenesis, apoptosis evasion, and the cell cycle. Primary and secondary metabolites that plants produce serve a variety of purposes. The ability of plants to produce a wide variety of secondary metabolites has led to human exploitation of these compounds for their usefulness in a wide range of applications. Secondary metabolites from plants are frequently referred to as natural products since they impact other living organisms. The main reasons terpenes have been used are their natural characteristics, such as their cytotoxicity, antibacterial, anti-inflammatory, analgesic, and insect-repellent actions. Acute and chronic diseases have been prevented and treated using specific essential oils because of their unique medicinal and therapeutic characteristics. Terpenes are a large class of naturally occurring hydrocarbon secondary metabolites comprising five-carbon isoprene units that can be constructed in various ways with varying degrees of unsaturation, oxidation, reduction, functional groups and ring closure. This results in a rich diversity of structural classes, continually discovering new skeletons. Three isoprene units make up sesquiterpenes, a subclass of terpenes with the chemical formula $C_{15}H_{24}$. Sesquiterpenes come in various unusual combinations since they can contain rings or be acyclic. Several small compounds have been authorized as anticancer medications based on natural products [8]. Three isoprene units plus one or more lactone rings condense to generate the natural chemical known as sesquiterpene lactones. One of their methanol groups had some isoprene group oxidized to lactones. It depends on the presence of the α-methylene-γ-lactone moiety for many sesquiterpene lactones to exhibit cytotoxicity against cancer cells. This functional group is an alkylating agent for biomolecules with nucleophilic groups in a Michael-type reaction. Multiple signal transduction pathways involved in cell death and survival are targeted by sesquiterpene lactones [8, 9, 10].

MATERIALS AND METHODOLOGY:

Protein Structure: From the protein data bank (PDB), the structural information for the Bcl-2 (PDB ID: 1GJH) and Bcl-xl (PDB ID: 1MAZ) proteins was retrieved and processed for further investigation.

Ligand Data: Arctigenin, Arthenolide C, Gaillardin, Helenalin, Ixerin D and Obatoclax were the phytocompounds whose 3D molecular structures were obtained from PubChem in SDF format and converted to PDB format using Open

Babel 3.1.1 software [12]. Obatoclax served as the study's control ligand. Obatoclax, a Bcl-2 inhibitor in pre-clinical testing, acts as an anti-apoptotic protein antagonist [11].

Docking Procedure: The PyRx 0.8 software was used for molecular docking [13]. By using blind docking, ligands, and target structures were docked at random or without consideration for the active site. The highest grid box value was set and docking was completed for each ligand. Using Discovery Studio, it was possible to examine the amino acid residues that each ligand binds to, save the file and see the binding affinity of the interaction. Discovery Studio provided a visual representation of the interplay between 2D and 3D.

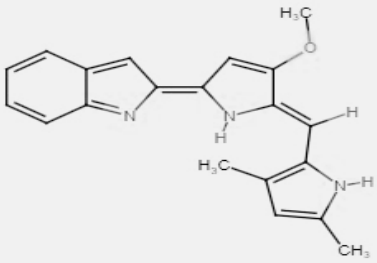
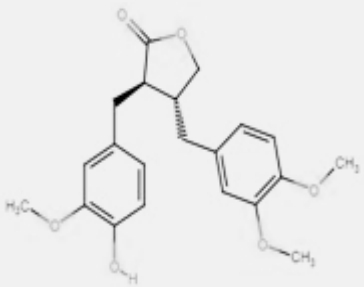
ADMET Predictions of Ligand: The targeted compound's Lipinski rule of five (Ro5) was measured using SwissADME software. According to the rule, most molecules with good membrane permeability have no more than five hydrogen bond donors and no more than ten hydrogen bond acceptors, a molecular weight of no more than 500 g/mol, a polar surface area of no more than 140 Å^2 and a calculated Log P (clogP) that is greater than five (or mlogP > 4.15). The anticipated octanol/water partition coefficient is mlogP. Additionally, SwissADME was used to determine the topological polar surface area (TPSA), which is the surface that polar atoms occupy. This descriptor has been proven to correlate well with passive molecule transport through membranes, allowing for the prediction of drug transport features [14].

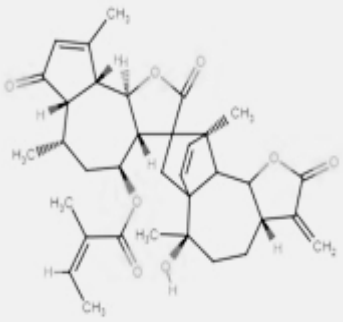
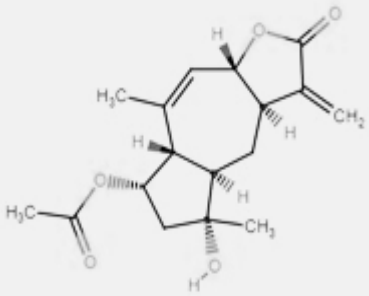
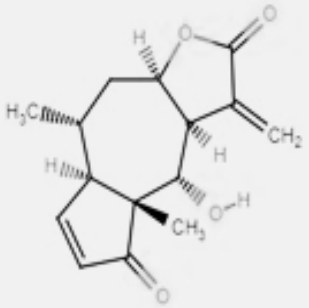
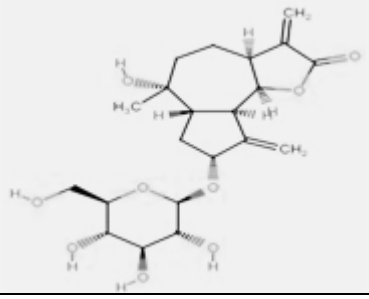
RESULT AND DISCUSSION:

Molecular Docking: The intrinsic process of apoptosis involves the proteins Bcl-2 and Bcl-xl, which are crucial. These two proteins have a role in the anti-apoptotic and survival mechanisms. Apoptosis can happen when Bax and Bak share homology in BH1-3 and the four-helical Bcl-2 domain (BH) BH1-4. Unfortunately, overe-xpression of the anti-apoptotic proteins Bcl-2 and Bcl-xl is consistently detected in cancer, thus it must be suppressed to maintain a balance with the changes toward the multi-domain pro-apoptotic proteins Bax and Bak.

The interaction of ligands and proteins was investigated using molecular docking. The interaction between bioactive substances and anti-apoptotic proteins was examined and rated based on the binding affinity. **Table 1** summarizes the analysis of this study's binding affinities (kcal/mol). The principal force-field-based function was the observation of binding affinity score. The less intermolecular force between the ligand and protein and the more permanent the association of the complex generated, the lower the binding affinity score.

TABLE 1: THE BINDING AFFINITY OF INVESTIGATED BIOACTIVE COMPOUNDS AGAINST BCL-2 AND BCL-XL PROTEINS

Ligand (PubChem ID)	Structure	Binding Affinity (Kcal/mol)	
		Bcl-2	Bcl-xl
Obatoclax (16681698)		-7.4	-7.7
Arctigenin (64981)		-6.4	-7.4

Arteminolide C (129010622)		-7.8	-8.9
Gaillardin (267247)		-6.3	-7
Helenalin (23205)		-6.7	-6.9
Ixerin D (101553163)		-6.9	-7.6

Binding Interaction with Bcl-2: Table 2 provides an overview of how the bioactive chemicals under investigation interacted with the Bcl-2 protein and which amino acid residues they affected. Results showed that the interaction of obatoclax and Bcl-2 protein consists of a hydrogen bond, an electrostatic, and a hydrophobic bond.

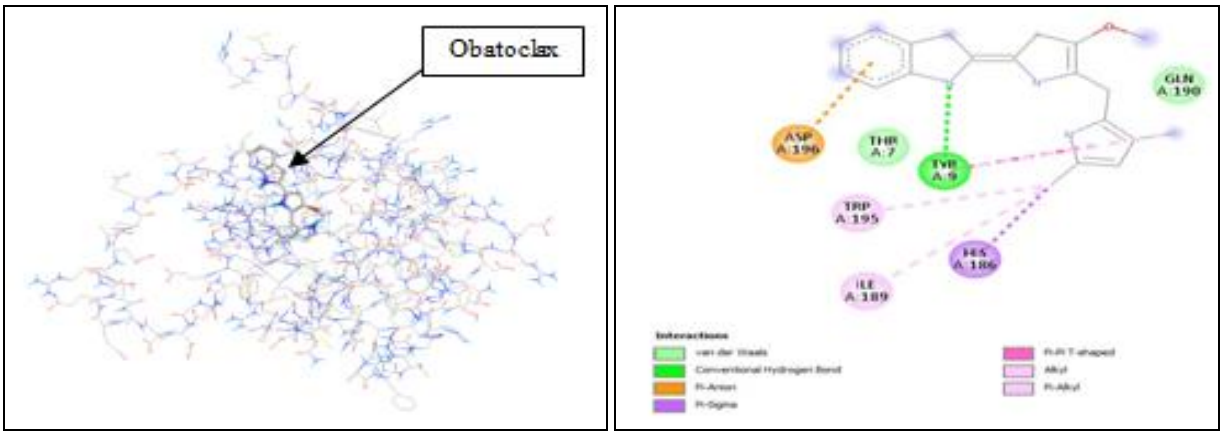
However, a hydrogen bond was formed involving amino acid residue THR A:09 as a conventional hydrogen bond. In contrast, the three hydrophobic interactions were formed involving hydrophobic amino acids THR A:09, TRP A:195, ILE A:189 and HIS A:186 as Pi-Pi T-shaped, Pi-Alkyl, Alkyl, Pi-Sigma interactions. Arctigenin form four hydrogen bond by amino acid residue THR A:07, GLY A:08, TYR A:09, and ASN A:11 as a conventional hydrogen bond, and three hydrophobic interactions were formed involving amino acids TRP A:195 and HIS A:186 as Pi-Pi T-shaped and Pi-Alkyl. Ixerin D forms six hydrogen bonds by amino acid residue SER A:49, GLY A:46, THR A:07, GLU A:48, GLU A:45, GLU A:13 as a conventional hydrogen bond. As a conventional hydrogen bond, Gaillardin forms one hydrogen bond by amino acid residue LEU A: 137.

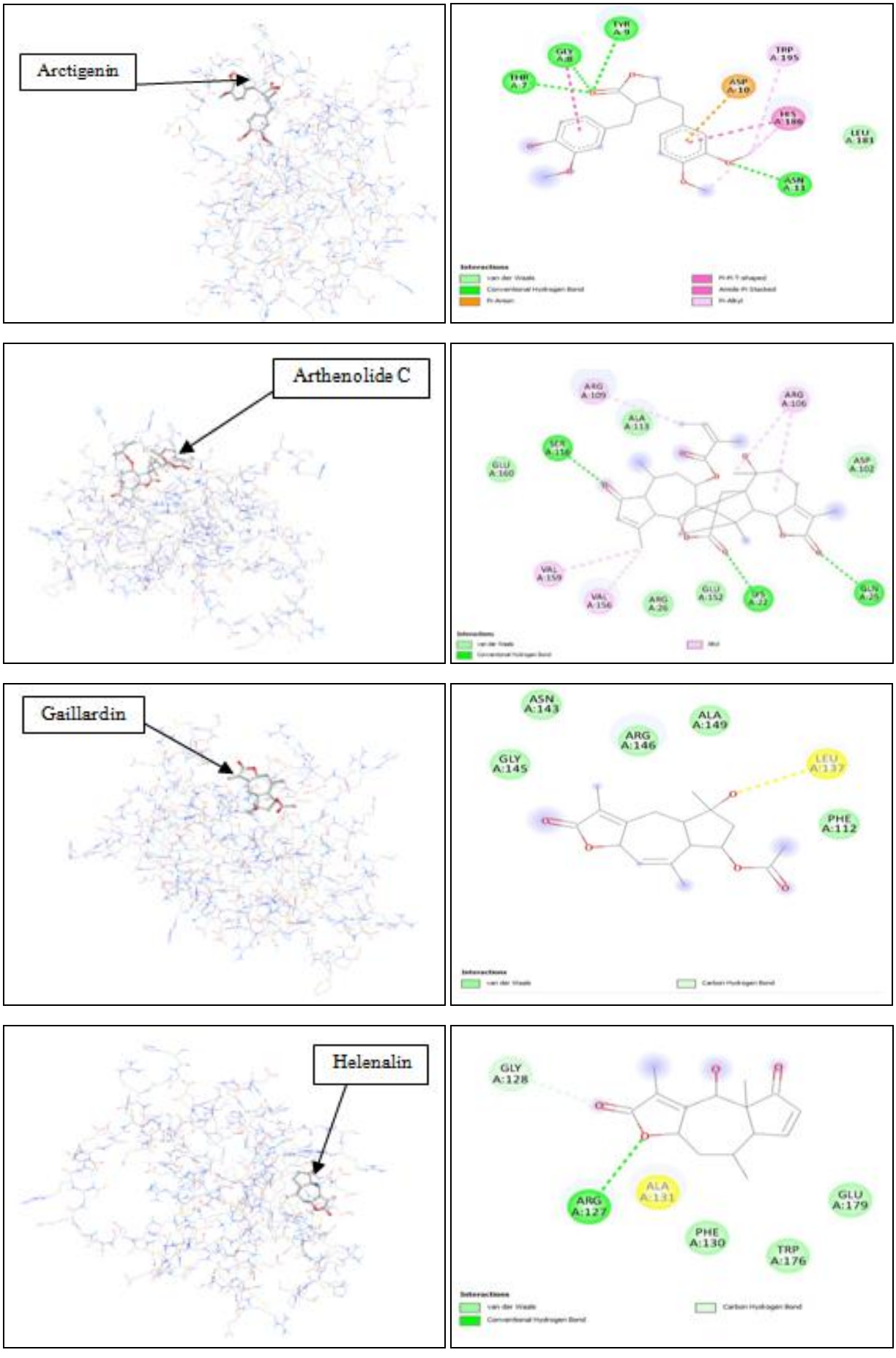
Helenalin forms two hydrogen bonds by amino acid residue GLY A:128 and ARG A:127 as a carbon and conventional hydrogen bond, respectively. Arthenolide C forms three hydrogen bond by amino acid residue SER A:116, GLN

A:106, LYS A:22 as a conventional hydrogen bond and five hydrophobic interactions were formed involving amino acids ARG A:109, VAL A:159, VAL A:156, ARG A:106:C, ARG A:106 as Alkyl. The ligand-protein complex's selectivity is increasingly attributed to the hydrogen bond and hydrophobic interaction, which are basic and increasingly important. Most docking and scoring were performed while carefully examining the binding interaction based on hydrogen bonds.

TABLE 2: INTERACTION AND AMINO ACID RESIDUES INVOLVEMENT OF INVESTIGATED BIOACTIVE COMPOUNDS AGAINST BCL-2 PROTEIN

Receptor-ligand Docked complex	Interacting Residues	Bond distance (A)	Category	Type of bond
Obatoclax—bcl-2	ASP A:196	3.86	Electrostatic	Pi-Anion
	THR A:09	3.39	Hydrogen bond	Conventional hydrogen bond
		5.41	Hydrophobic	Pi-Pi T-shaped
		5.20	Hydrophobic	Pi-Alkyl
	TRP A:195	4.32	Hydrophobic	Pi-Alkyl
	ILE A:189	4.90	Hydrophobic	Alkyl
	HIS A:186	3.82	Hydrophobic	Pi-Sigma
Arctigenin—Bcl-2	THR A:7	2.16	Hydrogen bond	Conventional hydrogen bond
	GLY A:08	4.25	Hydrophobic	Amide-Pi Stacked
		1.80	Hydrogen bond	Conventional hydrogen bond
	TYR A:09	2.63	Hydrogen bond	Conventional hydrogen bond
	ASP A:10	4.34	Electrostatic	Pi-Anion
	TRP A:195	4.36	Hydrophobic	Pi-Alkyl
	HIS A:186	4.42	Hydrophobic	Pi-Pi T-shaped
		4.44	Hydrophobic	Pi-Alkyl
	ASN A:11	2.19	Hydrogen bond	Conventional hydrogen bond
Ixerin D—Bcl-2	SER A:49	2.34	Hydrogen bond	Conventional hydrogen bond
	GLY A:46	2.63	Hydrogen bond	Conventional hydrogen bond
	THR A:07	3.13	Hydrogen bond	Carbon hydrogen bond
	GLU A:48	2.74	Hydrogen bond	Conventional hydrogen bond
	GLU A:45	2.00	Hydrogen bond	Conventional hydrogen bond
	GLU A:13	2.19	Hydrogen bond	Conventional hydrogen bond
Gaillardin—Bcl-2	LEU A:137	2.87	Hydrogen bond	Conventional hydrogen bond
Helenalin—Bcl-2	GLY A:128	2.53	Hydrogen bond	Carbon hydrogen bond
	ARG A:127	2.82	Hydrogen bond	Conventional hydrogen bond
Arthenolide C—Bcl-2	SER A:116	2.54	Hydrogen bond	Conventional hydrogen bond
	ARG A:109	4.16	Hydrophobic	Alkyl
	GLN A:106	3.21	Hydrogen bond	Conventional hydrogen bond
	LYS A:22	2.33	Hydrogen bond	Conventional hydrogen bond
	VAL A:159	3.92	Hydrophobic	Alkyl
	VAL A:156	3.66	Hydrophobic	Alkyl
	ARG A:106:C	5.49	Hydrophobic	Alkyl
	ARG A:106	4.76	Hydrophobic	Alkyl




Arctigenin
TYR A:9
GLY A:8
THR A:7
TRP A:195
ASP A:10
HIS A:180
LEU A:181
ASN A:11
Arthenolide C
ARG A:109
ALA A:113
SER A:116
GLU A:160
ARG A:106
ASP A:102
VAL A:159
VAL A:156
ARG A:26
GLU A:152
LYS A:22
GLN A:25
Gaillardin
ASN A:143
ALA A:149
ARG A:146
GLY A:145
LEU A:137
PHE A:112
Helenalin
GLY A:128
ARG A:127
ALA A:131
PHE A:130
TRP A:176
GLU A:179

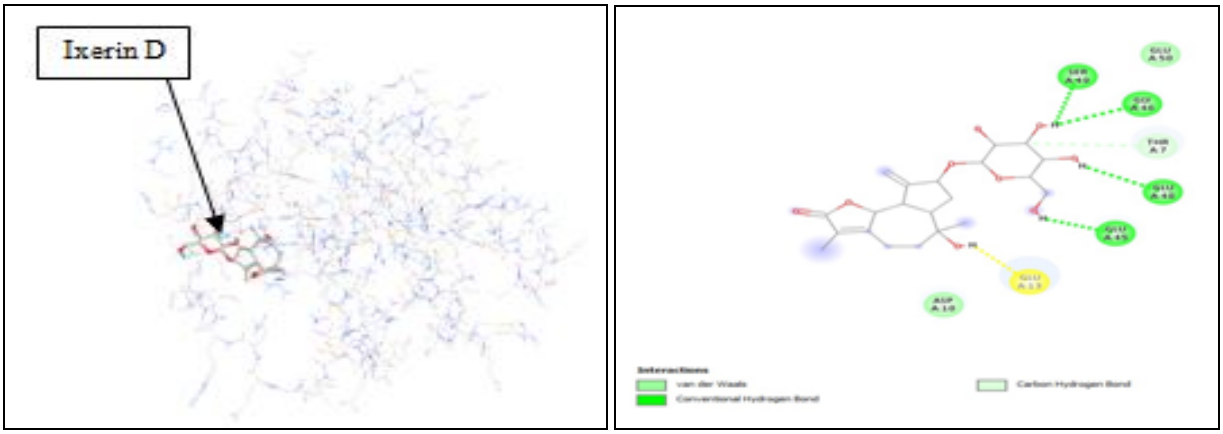


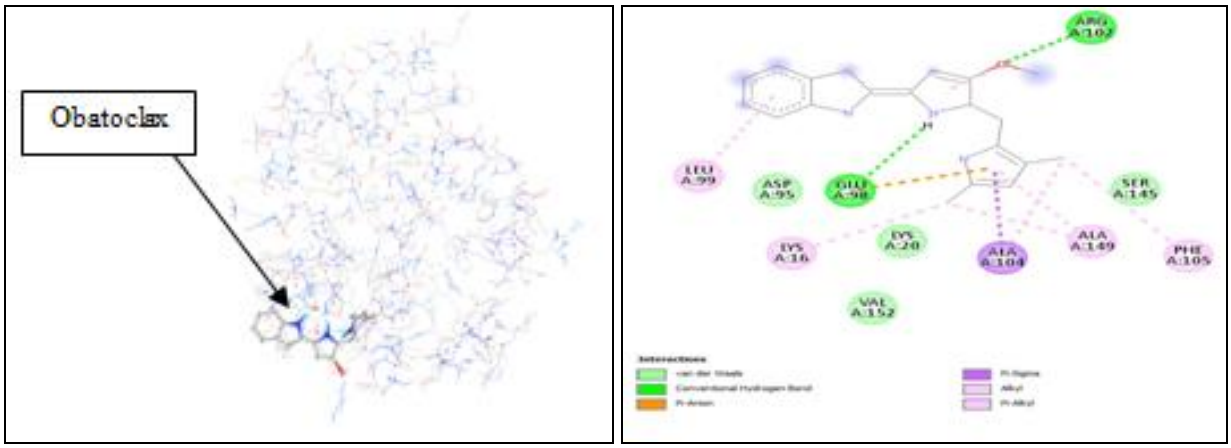
FIG. 1: INVESTIGATED BIOACTIVE PHYTOCOMPOUNDS INTERACTIONS WITH THE BCL-2 PROTEIN

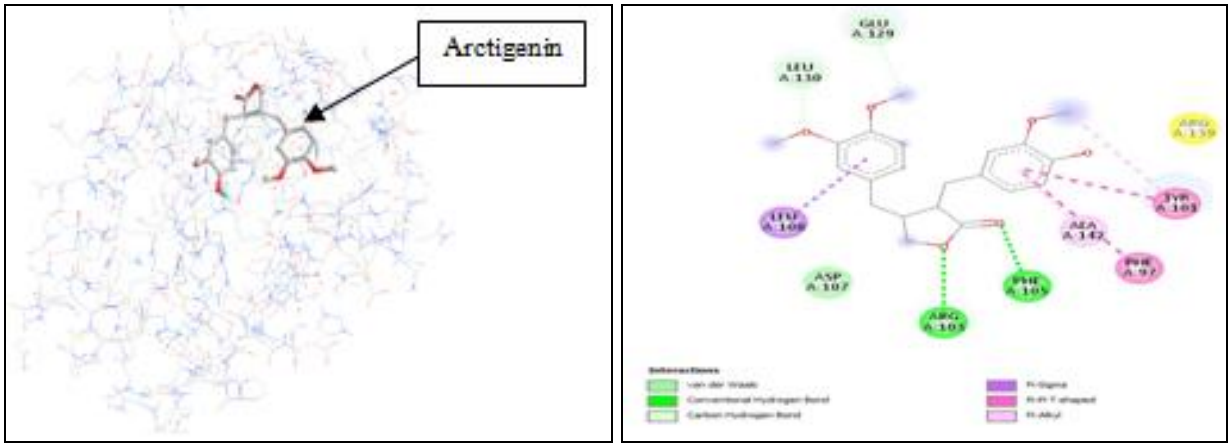
Binding Interaction with Bcl-xl: Table 3 provides an overview of how the bioactive substances under investigation interacted with the Bcl-xl protein and which amino acid residues they affected. Results showed that the interaction of obatoclax and Bcl-xl protein consists of a hydrogen bond, an electrostatic, and a hydrophobic bond. Amino acid residue ARG A:102 and and GLU A:98 was involved in hydrogen bond as conventional hydrogen bond interaction. Hydrophobic interaction formed involving amino acid residues ARG A:102, LEU A:99, GLU A:98, LYS A:16, ALA A:149, PHE A:105 as Alkyl and Pi-Alkyl interaction. Arctigenin and Bcl-xl interaction consists of four hydrogen bonds and four hydrophobic interactions involving amino acid residues GLU A:129, LEU A:130, ARG A:103, PHE A:105, LEU A:108, ALA A:142, PHE A:97 and TRY A:101. The type of interaction formed includes conventional hydrogen bond, Pi-Sigma, Pi-Pi T-Shaped and Pi Alkyl. Ixerin D form three hydrogen bond by amino acid residue ALA A:145, ASN A:136, ARG A:139 as a conventional hydrogen bond, and one hydrophobic interaction were form involving amino acids PHE A:105 as Pi-Alkyl. Gaillardin form two hydrogen bond by amino acid residue ARG A:103:NE, ARG A:103: NH2 as a conventional hydrogen bond. Helenalin form two hydrogen bonds by amino acid residue ARG A:103:NE, ARG A:103: NH2 as a conventional hydrogen bond and hydrophobic interaction involving amino acids PHE A:105 as Pi-Sigma. Arthenolide C forms one hydrogen bond by amino acid residue ARG A:103 as a conventional hydrogen bond, and hydrophobic interaction was formed involving amino acids PHE A:105 as Pi-Sigma. The ligand-protein complex's selectivity is increasingly being attributed to the hydrogen bond and hydrophobic interaction, which are basic and increasingly important. Most docking and scoring were performed while carefully examining the binding interaction based on hydrogen bonds.

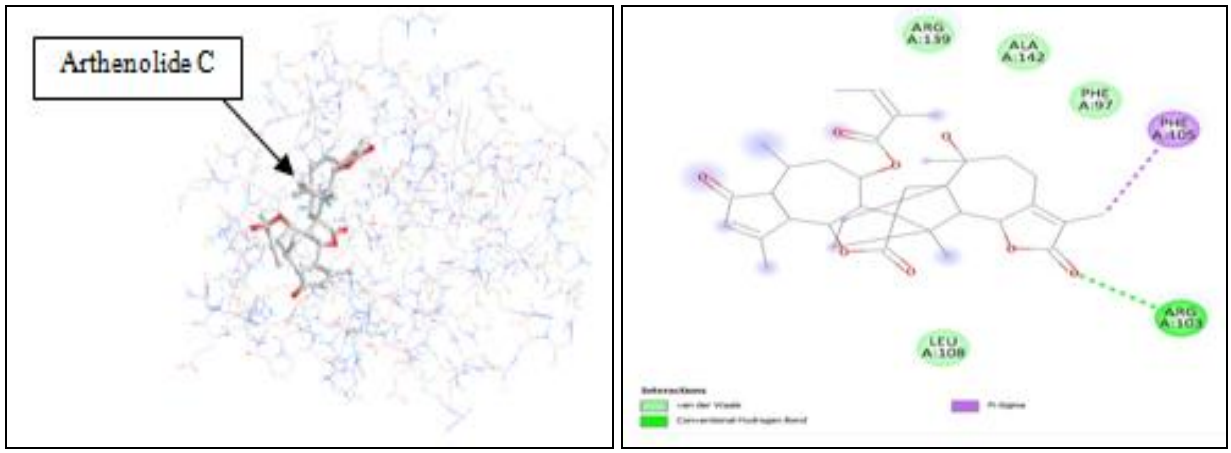
TABLE 3: INTERACTION AND AMINO ACID RESIDUES INVOLVEMENT OF INVESTIGATED BIOACTIVE COMPOUNDS AGAINST BCL-XL PROTEIN

Receptor-ligand Docked complex	Interacting Residues	Bond distance (A)	Category	Type of bond
Obatoclax—bcl-xl	ARG A:102	3.24	Hydrogen bond	Conventional hydrogen bond
		4.61	Hydrophobic	Pi-Alkyl
	LEU A:99	4.84	Hydrophobic	Pi-Alkyl
	GLU A:98	2.85	Hydrogen bond	Conventional hydrogen bond
		3.78	Electrostatic	Pi-Anion
	LYS A:16	4.34	Hydrophobic	Alkyl
	ALA A:149	4.12	Hydrophobic	Alkyl
		4.48	Hydrophobic	Pi-Alkyl
	PHE A:105	4.63	Hydrophobic	Pi-Alkyl
Arctigenin—Bcl-xl	GLU A:129	3.52	Hydrogen bond	Conventional hydrogen bond
	LEU A:130	3.57	Hydrogen bond	Conventional hydrogen bond
	LEU A:108	3.85	Hydrophobic	Pi-Sigma
	ARG A:103	2.87	Hydrogen bond	Conventional hydrogen bond

	PHE A:105	3.24	Hydrogen bond	Conventional hydrogen bond
	ALA A:142	4.30	Hydrophobic	Pi-Alkyl
	PHE A:97	5.01	Hydrophobic	Pi-Pi T-shaped
	TRY A:101	4.88	Hydrophobic	Pi-Alkyl
Ixerin D—Bcl-xl	PHE A:105	5.00	Hydrophobic	Pi-Alkyl
	ALA A:145	3.25	Hydrogen bond	Conventional hydrogen bond
	ASN A:136	2.19	Hydrogen bond	Conventional hydrogen bond
	ARG A:139	3.21	Hydrogen bond	Conventional hydrogen bond
Gaillardin—Bcl-xl	ARG A:103:NE	3.14	Hydrogen bond	Conventional hydrogen bond
	ARG A:103:NH2	2.91	Hydrogen bond	Conventional hydrogen bond
Helenalin—Bcl-xl	PHE A:105	3.86	Hydrophobic	Pi-Sigma
	ARG A:103:NE	3.09	Hydrogen bond	Conventional hydrogen bond
	ARG A:103:NH2	3.15	Hydrogen bond	Conventional hydrogen bond
Arthenolide C—	PHE A:105	3.81	Hydrophobic	Pi-Sigma
Bcl-xl	ARG A:103	2.90	Hydrogen bond	Conventional hydrogen bond







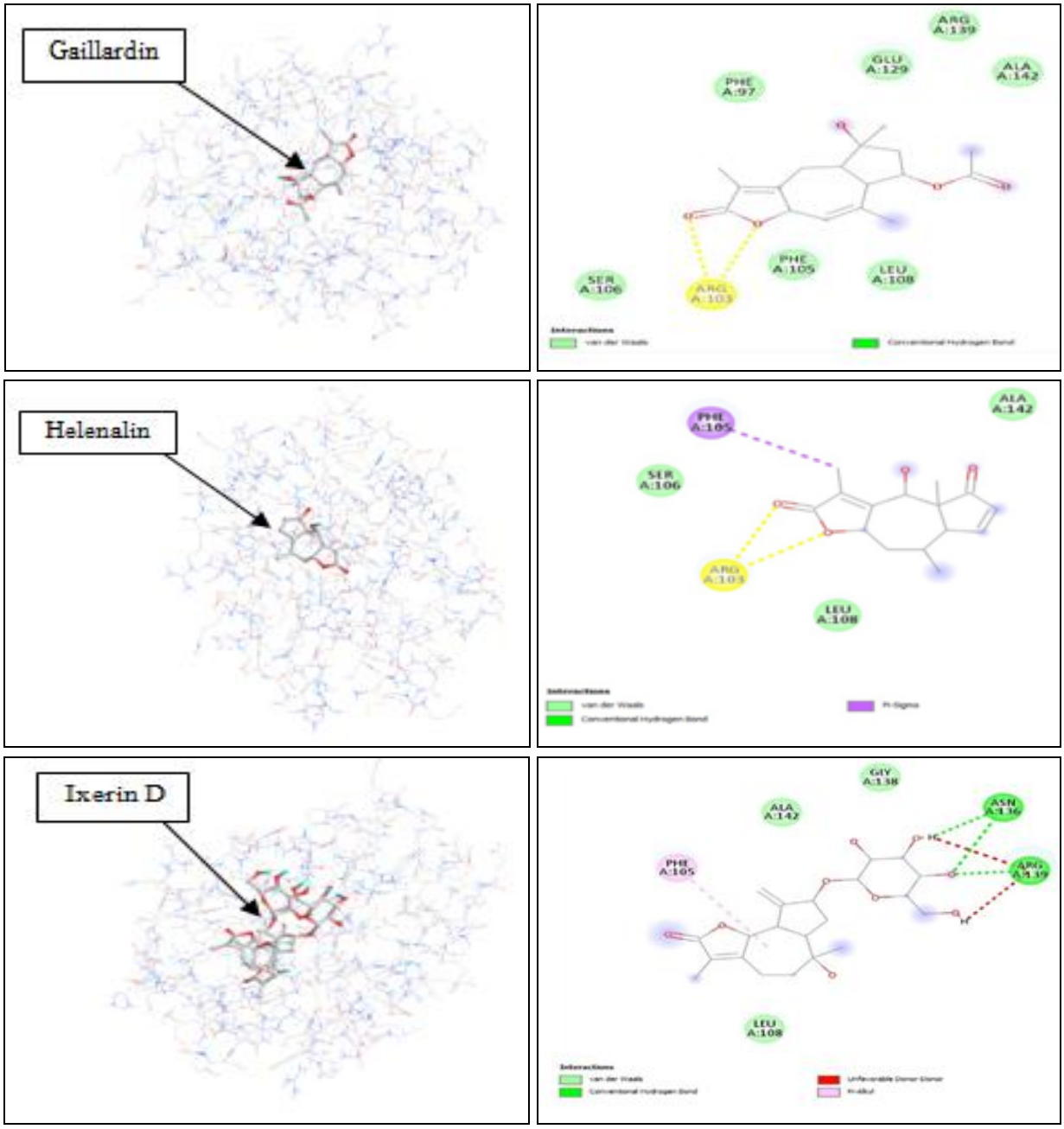


FIG. 2: INTERACTION OF INVESTIGATED BIOACTIVE COMPOUNDS TOWARD BCL-XL PROTEIN

ADMET Prediction of Ligands: Results of the calculations for the molecules in this study show that all molecules have the potential for good *in-vivo* absorption except one that is Arteminolide C, since all the compounds show zero violation of the rule, whereas Arteminolide C has a molecular weight more than 500g/mol were summarized in **Table 4.**

TABLE 4: PHYSICOCHEMICAL PROPERTIES PREDICTED BY SWISSADME

Compounnd	MF	MW (g/mol)	nRB	nHBA	nHBD	TPSA (Å²)	mlogP	Ro5
Obatoclax	$C_{20}H_{19}N_3O$	317.38	2	2	2	53.17	3	0
Arctigenin	$C_{21}H_{24}O_6$	372.41	7	6	1	74.22	3.1	0
Arteminolide C	$C_{35}H_{42}O_8$	590.7	3	8	1	116.20	4.13	1
Gaillardin	$C_{17}H_{22}O_5$	306.35	2	5	1	72.83	1.82	0
Helenalin	$C_{15}H_{18}O_4$	262.3	0	4	1	63.60	1.37	0
Ixerin D	$C_{21}H_{30}O_9$	426.46	3	9	5	145.91	-0.09	0

Abbreviations: MF: molecular formula; mlogP: predicted octanol/water partition coefficient; MW: molecular weight; nRB: number of rotatable bond; nHBA: number of hydrogen bond acceptors; nHBD: number of hydrogen bond donors; TPSA: topological polar surface area; Ro5: Lipinski violations.

CONCLUSION: According to the results of the docking research, five phytocompounds, such as Arctigenin, Arteminolide C, Gaillardin, Helenalin, and Ixerin D, had a binding affinity score against anti-apoptotic proteins Bcl-2 and Bcl-xl comparable to that of obatoclax. Both anti-apoptotic proteins and bioactive chemicals created a binding relationship that revealed more hydrogen and hydrophobic interactions. As a result, we reported Bcl-2 binding characteristics of investigated phytochemicals for further evaluation and *in-vitro* and *in-vivo* validation.

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