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A Computational Modeling Study on the Biomolecular Interactions of the Phytoconstituents of *Nigella sativa* with Anti-Apoptotic Proteins Mcl-1 and Bcl-x1

Olajumoke B. Oladapo [a*], Toheeb A. Jumah [b], Justine U. Egbe [c], Jude O. Uzoechina [d], Aderonke E. Fakayode [e], Muhammad I. Adeyemi [f], Oluwaseyi P. Olaniyan [g], Chimunda A. Solomon [h], Zion O. Oluwasegun [i], Damilola M. Olatunde [j], Uche O. Arunsi [k], Samuel O. Olubode [l,m*], Precious A. Akinnusi [l,m], Toheeb A Balogun [l,m], Sunday B. Akinde [n]

[a] Department of Cell Biology and Genetics, University of Lagos, Nigeria.
[b] School of Collective Intelligence, Mohammed VI Polytechnic University, Morocco.
[c] Nigerian Institute of Medical Research (NIMR) Lagos Nigeria.
[d] Department of Biochemistry, University of Nigeria, Nsukka, Nigeria.
[e] Medical College of Georgia, Augusta University
[f] Department of Biochemistry and Molecular Biology, Usmanu Danfodiyo University Sokoto, Nigeria.
[g] Multidisciplinary Research Laboratory, Osun State University, Nigeria
[h] Pharmacology and therapeutics, University of Lagos, Nigeria.
[i] Department of Biochemistry, Federal University of Technology, Akure, Nigeria and Digital Health, Africa.
[j] Department of Biochemistry, Federal University of Technology Akure, Nigeria.
[k] School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, USA.
[l] Institute of Bioinformatics and Molecular Therapeutics (IBMT), Osogbo, Osun State, Nigeria.
[m] Department of Biochemistry, Adekunle Ajasin University Akungba, Ondo State Nigeria.
[n] Multidisciplinary Research Laboratory, Osun State University, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Authors OBO, SOO, PAA and TAB conceptualized, supervised the study and edited the final manuscript draft. Authors TAJ, AEF, JOU, and JUE performed the experiment. Authors OBO, CAS, ZOO DMO, AEF and UOA mined the data for the experiment and analyzed the experiment results. Authors MIA, SBA, OBO and OPO wrote the original manuscript. All authors read and approved the final manuscript.

**Corresponding author: E-mail: olajumokeoladapo29@gmail.com; olubodesamuelolawale@gmail.com;*

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ABSTRACT

Cancer is the second leading cause of mortality worldwide. The strictly controlled physiological process of apoptosis is required for immune system function, maintenance of tissue homeostasis, and appropriate embryonic development. Anti-apoptotic proteins such as Bcl-xL and Mcl-1 are potent new anticancer targets. The inhibitory effect of the apparently therapeutic plant Nigella sativa on these targets is investigated using a molecular modeling approach in this work. From the molecular docking, we predict that seven compounds; apigenin, chlorogenic acid, hesperidin, quercetin, quercitrin, kaempferol, and rutin may have greater inhibitory potential against the target protein. These compounds have higher docking scores thus indicating higher binding affinities when compared to co-crystallized compounds. The co-compounds were crystallized with the standards, which served as the baselines for comparison studies. This result shows that that Nigella sativa compounds may be a potential anticancer drug that targets the anti-apoptotic protein. Targeting anti-apoptotic proteins provides clinical studies with the opportunity to evaluate for possible anti-cancer potential in the plant via other experimental models like rats and cancer cell lines. Using phytomedicines can equally augment existing therapy to provide synergistic anti-cancer effect when combined with existing drugs thereby enhancing therapy efficacy and because medicinal plants has lots of phytoconstituents, its use in this research can provide benefits of targeting multiple anti-apoptotic proteins thereby enhancing therapeutic effect unlike some conventional drugs that are mostly single targeting.

Keywords: Anti-apoptotic proteins; Mcl-1, Bcl-xL; molecular docking; ADMET; Nigella sativa.

ABBREVIATIONS

Mcl-1 : Myeloid cell leukemia-1;
Bcl-xl : B-cell lymphoma-extra-large;
ADMET : Absorption, Distribution, Metabolism, Excretion, and
Toxicity : XP – Extra precision;
PSA : Polar Surface Area

1. INTRODUCTION

Cancer is second only to myocardial infarction and other cardiovascular disorders as the leading cause of death worldwide. Recent worldwide epidemiology estimates that lung cancer kills roughly 2 million people a year [1] with men being more likely to be diagnosed than women. Tumor suppressor genes and oncogenes are positively impacted by the dysregulation of cellular, physiological, genetic, and epigenetic processes that underlie cancer [2,3].

Normal embryonic development, genomic integrity preservation, immune system function, and tissue homeostasis maintenance all rely on apoptosis, which is a closely regulated physiological process [4,5]. Mild doses of radiation, hypoxia, heat, cytotoxic drugs, or more targeted anti-cancer compounds all promote apoptosis [6]. Since the contents of the cell are eventually absorbed by phagocytic cells, the apoptotic route does not promote inflammation [7]. Apoptosis can be triggered by two distinct pathways: the intrinsic or mitochondrial pathway, which is triggered by intracellular stress signals such oxidative stress, and the extrinsic or death receptor pathway, which is triggered by extracellular signals [8]. The ratio of pro-apoptotic to anti-apoptotic proteins is a key regulator of the fundamental cellular apoptotic pathways studied in cancer therapy [9]. Some anti-apoptotic proteins, such as B-cell lymphoma

2, B-cell lymphoma extra-large, and Myeloid cell leukemia-1 (Bcl-2, Bcl-xL, and Mcl-1) [10, 11] have been shown to be effective novel anticancer targets. Although Bcl-xL and Bcl-2 are the same proteins, their roles as anti-apoptotic proteins are modulated in different ways by the signals that regulate them. Furthermore, Bcl-2 and Bcl-xL levels are inversely related to cancer risk [12]. Chemotherapy-resistant tumor cells express high amounts of Bcl-xL [13] and can be detected in many different types of solid tumors and some types of leukemia and malignant lymphoma. Cell migration, metastasis, and mitochondrial metabolism are some additional pathways that Bcl-xL may affect (Bessou *et al*., 2020). Based on the findings of structural analysis of the Bcl-xL protein, the first Bcl-2 family inhibitors and FDA-approved drugs were produced and introduced to the market (Chung *et al*., 2020). Tumorigenesis and cancer chemotherapy resistance are both facilitated by Bcl-XL's anti-apoptotic protein function, making it a promising target for cancer treatment [10]. Mcl-1 (Myeloid cell leukemia-1) is an important regulator of mitochondrial homeostasis and a member of the Bcl-2 family of anti-apoptotic proteins [14]. By interfering with a series of events that culminate in the release of cytochrome-c from mitochondria, Mcl-1 plays a critical role in regulating apoptosis [15]. Activated by a wide variety of survival cues and rapidly downregulated during apoptosis [16] this protein has a short half-life and is tightly regulated. Affecting the protein's stability and function include ubiquitination, cleavage, and phosphorylation sites in Mcl-1's N-terminus [17]. Mcl-1 is an attractive target for cancer therapy since it is overexpressed in human primary and drug-resistant cancer cells [14].

According to Mofio *et al.* [18] *Nigella sativa* is a dicotyledonous plant in the Ranunculaceae family. *Nigella sativa* has been shown to offer numerous health benefits, including those related to cancer, inflammation, bacteria, diabetes, antioxidants, immunity, pain relief, muscle relaxation, bronchial dilation, and gastrointestinal health (Karacil, 2022). Numerous bioactivities of *Nigella sativa* seeds and extracts have been discovered through in vitro and in vivo studies [19]. Salehi *et al*., 2021).

The inhibitory potentials of phytochemicals from *Nigella sativa* on chosen anti-apoptotic targets are investigated here using molecular docking and an ADMET screening technique inside a molecular modeling framework.

2. MATERIALS AND METHODS

2.1 Protein Ligands and their Targets

Nigella sativa's bioactive components were extracted using the LigPrep program after being retrieved from the PubChem database. Then, at a pH of 7.2 + 0.2, their ionization states and tautomers were synthesized using the OPLS 2005 force field for optimization. (scheduled for 2017 Schrödinger's Cat release).

After importing the protein structures from the Protein Data Bank into Maestro, the protein production wizard was used to produce the Mcl-1 and Bcl-xl anti-apoptotic proteins. These proteins have PDB IDs of 6U6F and 2O1Y, respectively. Hydrogen was added to the proteins had their and their binding energies minimized by removing unneeded ligands and other bound moieties. Prime and Waters were used to supplement the missing side chains. Grid boxes were also built to the location of the co-crystallized ligands to help direct the automated docking procedure and identify the binding sites of the proteins. The grid box coordinates of the Mcl-1 protein was; x=-33.98, y=-7.33, z=-19.56 while that of the Bcl-xl protein was x=1.77, y=4.04, z=5.1.

2.2 Docking of Molecules

The Glide docking tool in Maestro 11.1 was used for the molecular docking process. After preparing the compounds, they were docked into an established grid of protein targets to look for strong inhibitory interactions. The results of the most thorough screening (XP) were retrieved for additional analysis.

2.3 ADMET/Tox Screening

The pharmacokinetics, drug-likeness, and toxicity of the hit compounds were investigated with the help of the online servers for the programs swissADME [20] and Pro-Tox II [21].

3. RESULTS

The computational studies which involve molecular docking and ADMET screening were carefully analyzed as shown in Tables 1, 2 and 3. Hit compound molecular interactions with Mcl-1 and Bcl-xL active site amino acid residues are shown in Fig. 1 and 2, respectively.

4. DISCUSSION

Molecular docking is often performed using *in silico* methods to anticipate the structure and interaction of the ligand-receptor complex. Typically, this is accomplished by testing the binding affinity of the protein to the ligand in its various conformations within the active region of the protein (Balogun *et al*., 2021).

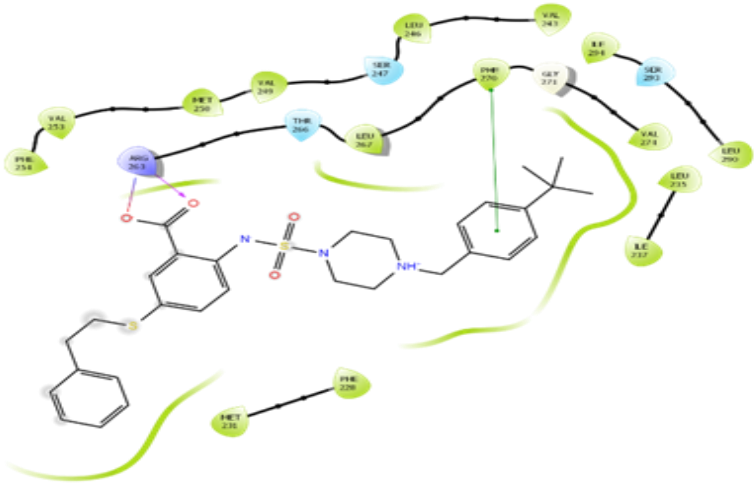
Computational analysis of the binding pocket of the anti-apoptotic proteins Mcl-1 and Bcl-xl was performed, and the results are displayed in the table above. Multiple studies have suggested that inhibiting anti-apoptotic Bcl-2 family members including Mcl-1 and Bcl-xl can be an effective treatment for cancer. More negative binding energy indicates a stronger binding affinity. When compared to the co-crystallized ligand of 6U6F, molecules from *Nigella sativa* exhibited greater negative energy during molecular docking, with a score of -7.85 kcal/mol. As can be seen in Table 1, the docking scores for the hit compounds range from -11.817 kcal/mol to -9.247 kcal/mol. *Nigella sativa* molecules docked with 201Y with a lower binding energy (-6.229 kcal/mol) than the co-crystallized ligand, according to the study. As can be seen in Table 2, the docking scores of the hit compounds vary from -8.311 to -6.439 kcal/mol.

Table 1. Molecular docking result of *Nigella sativa* and anti-apoptotic Mcl-1

Compounds	Docking score (Kcal/mol)	No of H-bond	Residue involved
CHEMBL4576854 (6u6f Ligand)	-7.85	2	ARG 263
Apigenin	-9.306	1	VAL 243
Chlorogenic acid	-11.817	4	VAL 243, ARG 263, THR 266
Hesperidin	-10.318	2	ASP 256
Quercetin	-9.615	2	LEU 246, THR 266
Quercitrin	-9.247	1	LEU 246

Table 2. Molecular docking result of *Nigella sativa* and anti-apoptotic Bcl-xL

Compounds	Docking score (Kcal/mol)	No of H-bond	Residue involved
CHEMBL1230221 (2o1y Ligand)	-6.229	1	ASN 140
Chlorogenic acid	-8.311	3	ALA 97, ALA 108, GLY 142
Hesperidin	-7.049	7	ALA 108, ASP 111, ARG 143, ASP 137, GLU 133
Kaempferol	-6.439	2	ALA 97, ASN 140
Quercitrin	-8.002	5	ALA 97, ASN 140, TYR 105, TYR 199
Rutin	-6.863	5	ARG 143, ASPV137, TYR 105



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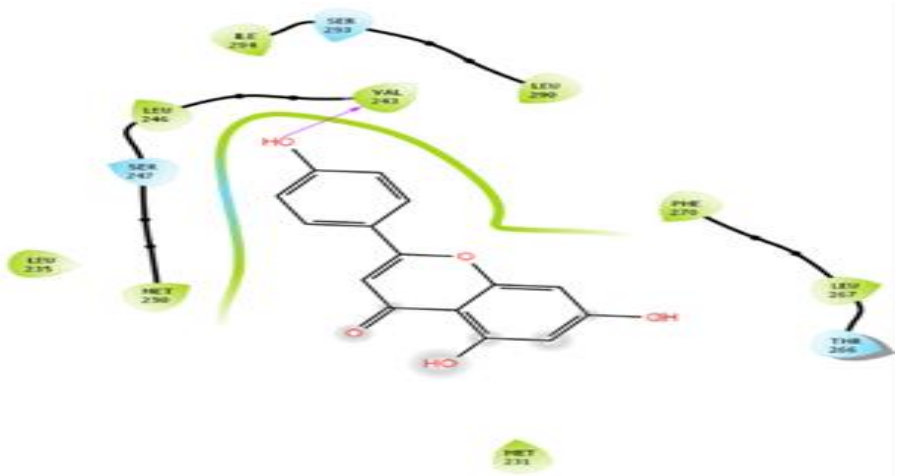

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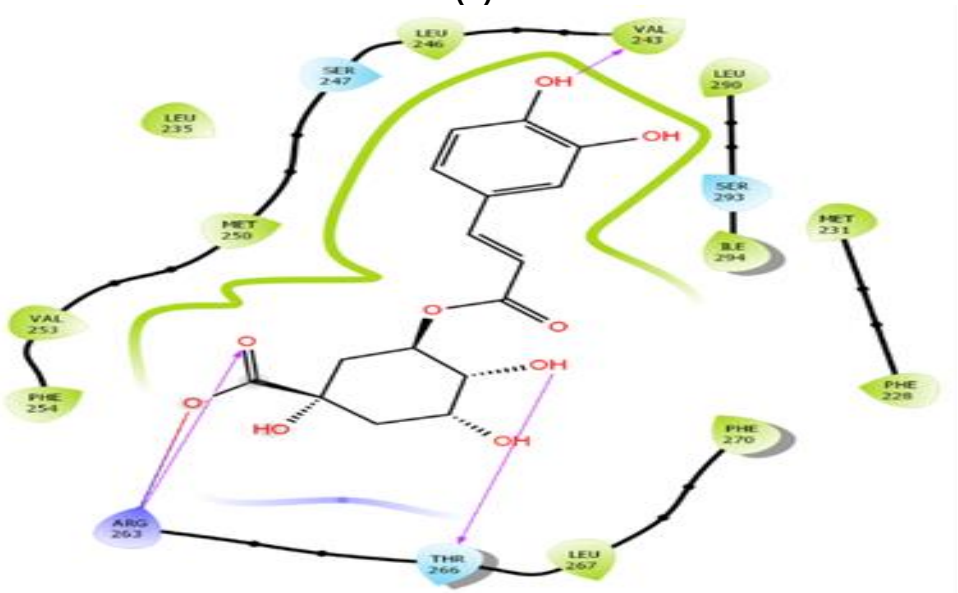

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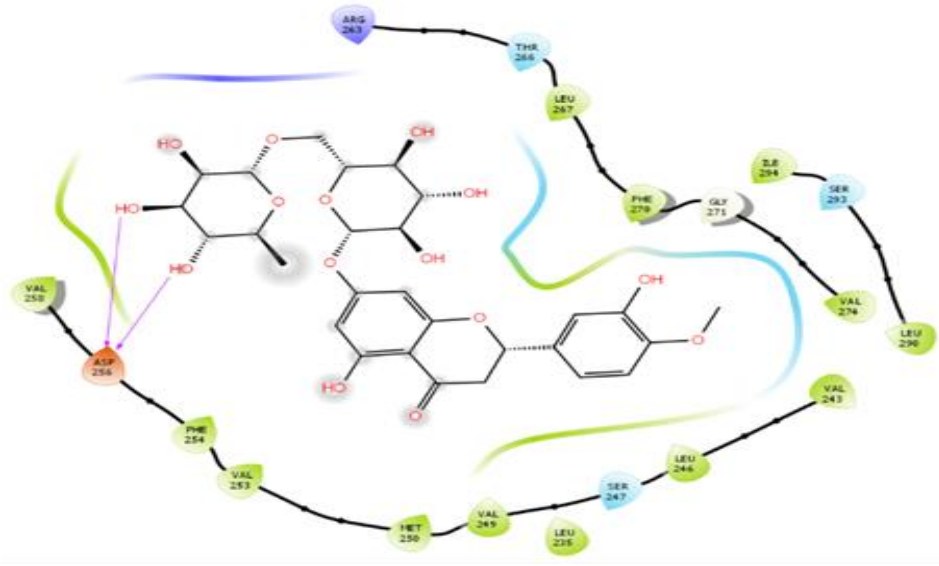

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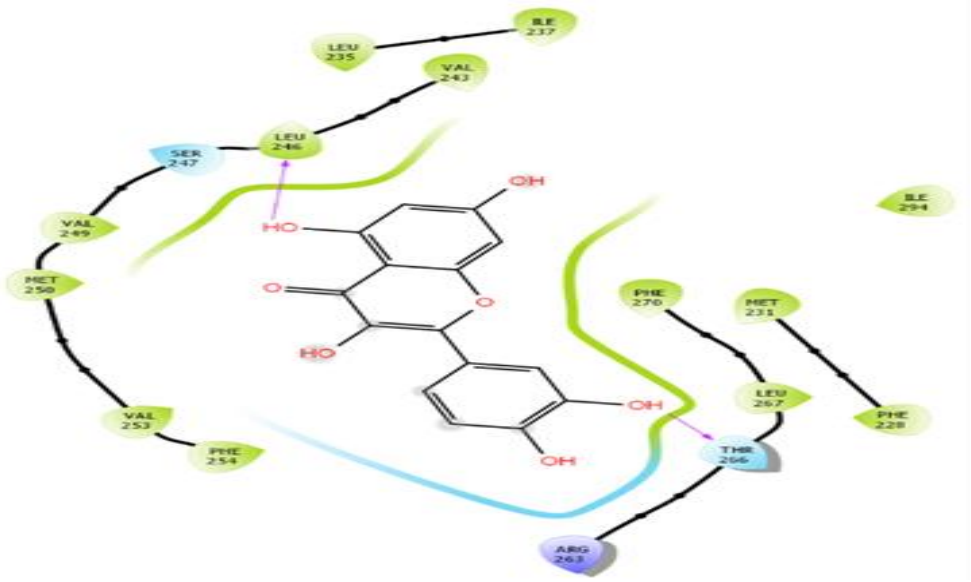

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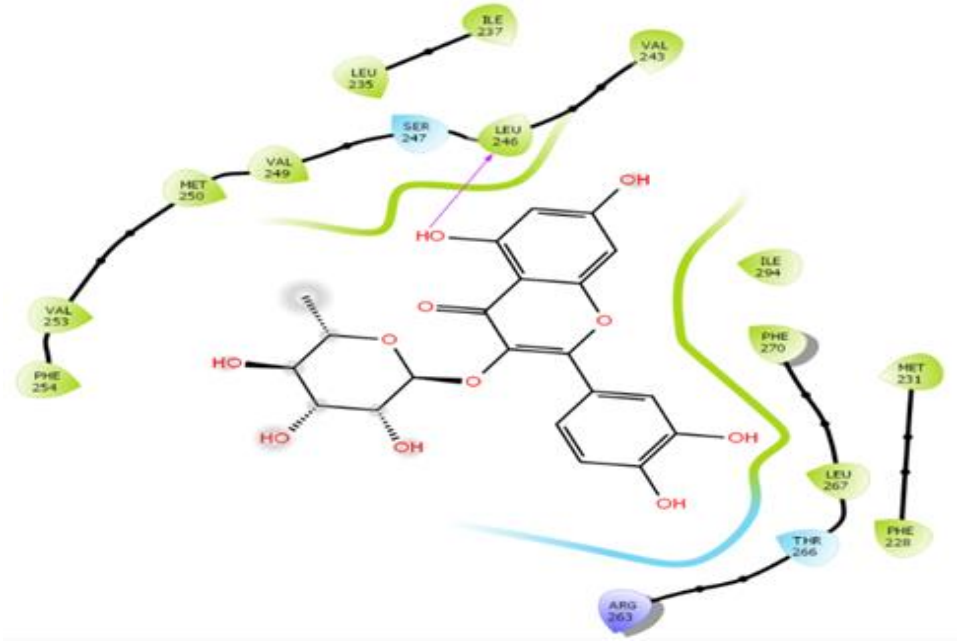

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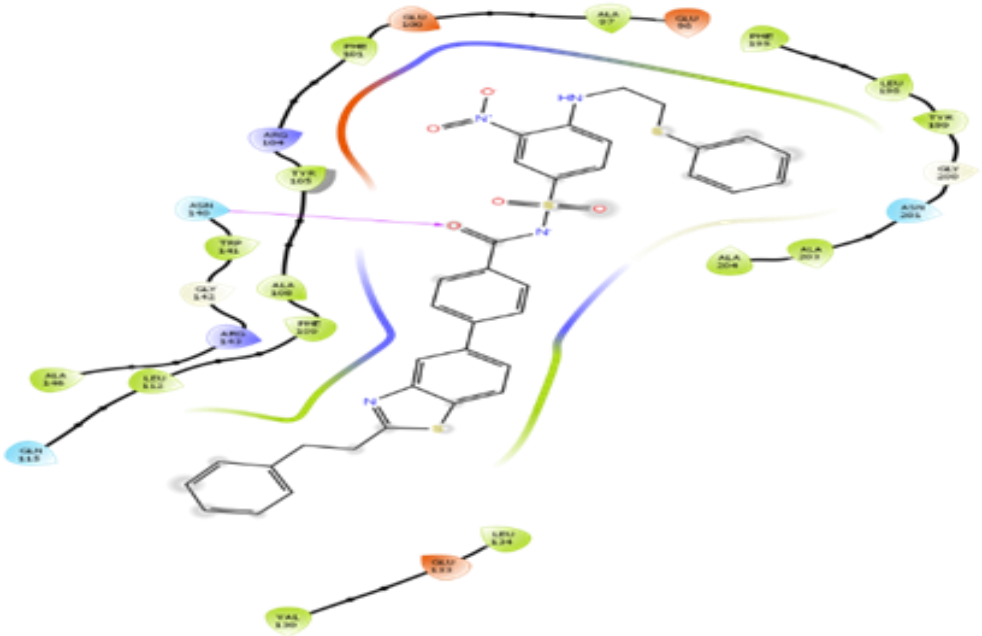
Fig. 1. 2D Molecular contacts profiling of docked compounds with amino acid residues at the active site of Mcl-1. (a) 6u6f ligand (b) Apigenin (c) Chlorogenic acid (d) Hesperidin (e) Quercetin (f) Quercitrin. The amino acid residue at the active site of the 6u6f ligand interaction with the target protein was ARG 263, the amino acid residues at the active site of the apigenin acid interaction was VAL 243, the amino acid residues at the active site of the chlorogenic acid interaction were VAL 243, ARG 263, THR 266, the amino acid residues at the active site of the hespiridin interaction was ASP 256, the amino acid residues at the active site of the quercetin interaction were LEU 246, THR 266, the amino acid residues at the active site of the quecitrin interaction was LEU 246

The binding energy of chlorogenic acid to Mcl-1 anti-apoptotic protein was the most negative (11.817 kcal/mol; Table 1), suggesting that it may have the most inhibitory capability among *Nigella sativa* compounds. Interacts with polar SER 247, SER 293, and THR 266, as well as hydrophobic LEU 235, LEU 246, LEU 267, LEU 290, MET 250, MET 231, VAL 253, VAL 243, PHE 254,

PHE 270, PHE 228, and ILE 294. Binding energy calculations for hesperidin (Table 1) suggest that it interacts primarily with the hydrophobic and polar amino acids in its immediate vicinity, including VAL 258, VAL 253, VAL 249, VAL 243, VAL 274, PHE 254, PHE 270, MET 250, LEU 235, LEU 246, LEU 290, LEU 267, ILE 294, THR 266, SER 293, and SER 247. While forming hydrogen bonding interactions with LEU 246 and THR 266, quercetin possessed a binding energy of 9.615 kcal/mol (Table 1). Fig. 1 shows that Apigenin and Quercitrin bind to Ser247, Ser293, Ser246, and Thr266 via hydrogen bonds and polar interactions, respectively, with binding energies of 9.306 and 9.247 kcal/mol (Table 1). These amino acid residues catalyze reactions by forming hydrogen bonds, van der Waals interactions, or pi-cation interactions, among other mechanisms.



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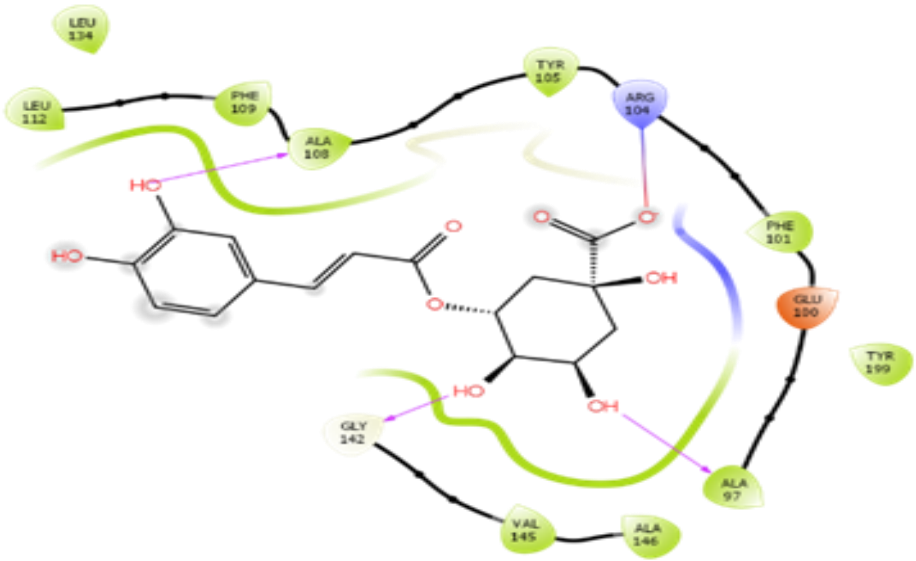

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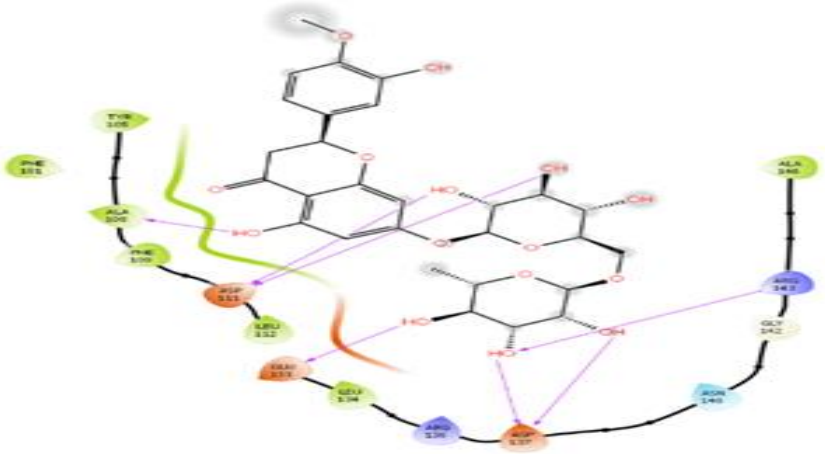

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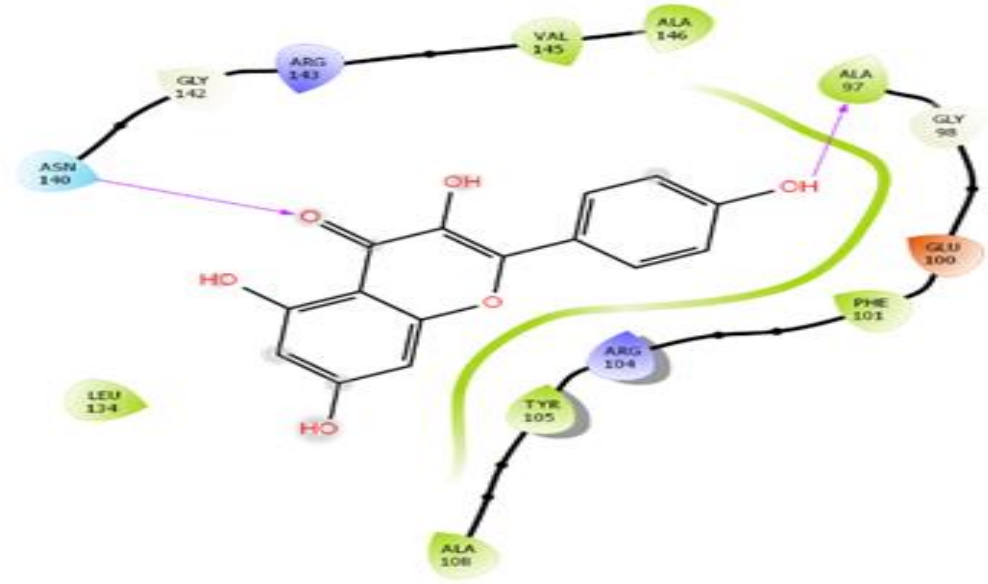
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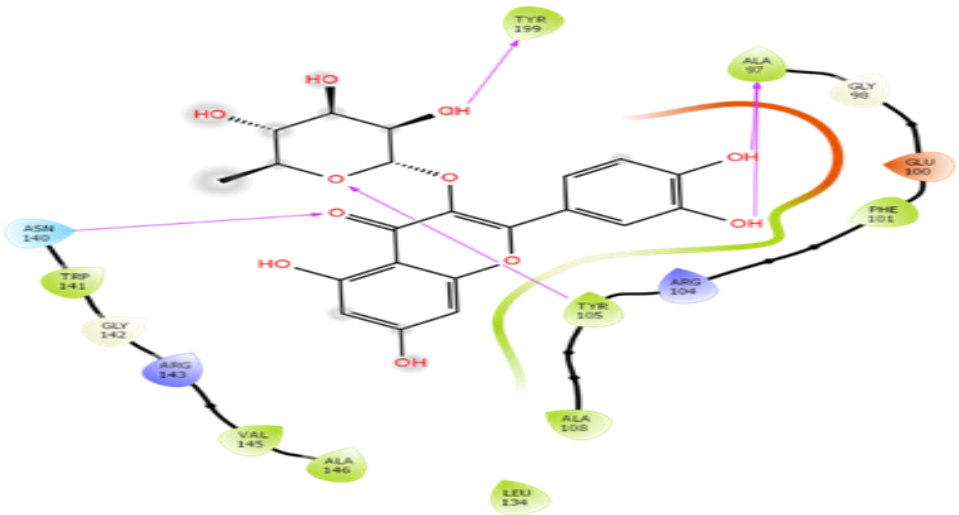
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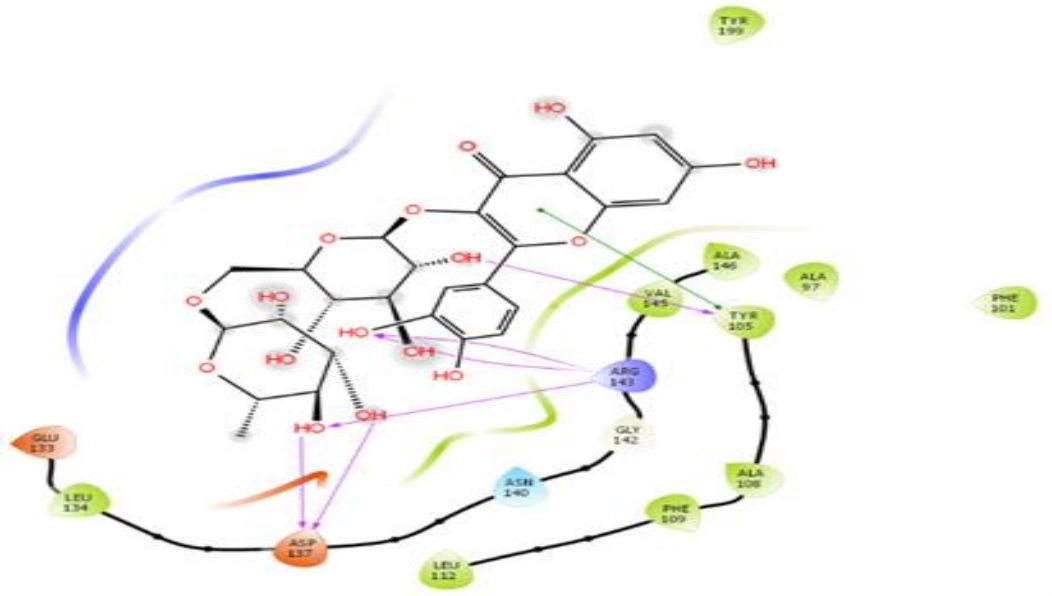

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Fig. 2. 2D molecular contacts profiling of docked compounds with amino acid residues at the active site of Bcl-xl: (a) 2O1Y ligand (b) Chlorogenic acid (c) Hespiridin (d) Kaempferol € Quercitrin (f) Rutin. The amino acid residue at the active site of the 2O1Y ligand interaction with the target protein was ASN 140, the amino acid residues at the active site of the chlorogenic acid interaction were ALA 97, ALA 108, GLY 142, the amino acid residues at the active site of the hespiridin interaction were ALA 108, ASP 111, ARG 143, ASP 137, GLU 133, the amino acid residues at the active site of the kaempferol interaction were ALA 97, ASN 140, the amino acid residues at the active site of the quercitrin interaction were ALA 97, ASN 140, TYR 105, TYR 199, the amino acid residues at the active site of the rutin interaction were ARG 143, ASPV137, TYR 105

However, the binding energy value of 8.311 kcal/mol revealed that Chlorogenic acid was the best bioactive molecule of *Nigella sativa* by docking results of *Nigella sativa* chemicals to the active site of Bcl-xl anti-apoptotic protein. It forms hydrogen bonds with the hydrophobic amino acids ALA-97 and ALA-108. Quercitrin, with a binding energy of 8.002 kcal/mol, is closely followed by the hydrophobic and polar amino acids TYR 199, TYR 105, TRP 141, VAL 145, ALA 146, ALA 108, ALA 97, LEU 134, PHE 101, ARG 143, ARG 104. Hesperidin formed hydrogen bonding interactions with ALA 108, ASP 111, ASP 137, GLU 133, and ARG 143, with a binding energy of 7.049 kcal/mol. Binding energies of 6.863 and 6.439 kcal/mol were observed for Rutin and Kaempferol, respectively, as they formed hydrogen bonds and polar interactions with TYR 105, ARG 143, ASP 137, ASN 140, and ALA 97.

In comparison to the co-crystallized ligands of 6U6F and 2O1Y, which served as standards for comparison, the molecular docking results suggest that chemicals from *Nigella sativa* may inhibit Mcl-1 and Bcl-xl anti-apoptotic proteins. Chlorogenic acid was shown to block both Mcl-1 and Bcl-xl, two proteins that normally protect cells from being destroyed by apoptosis.

4.1 Evaluation of ADMET Properties

Drug-likeness refers to the degree to which a potential drug exhibits properties that are analogous to those of currently available medications. Predicting whether or not a molecule has drug-like properties is crucial in many pharmacological fields since it allows for more precise targeting of promising molecules and less wasteful time spent on spurious hits. The bioavailability, protein affinity, toxicity, transport, absorption, and metabolic stability of a compound are all influenced by its chemical structure [22,23]. This is because of the compound's hydrophobicity, electronic distribution, hydrogen bonding, molecule size, and flexibility. In medicinal chemistry, ADME plays a crucial role in determining which

compounds are therapeutic candidates (Kumar *et al*., 2022). The docked compounds' drug-likeness, Lipinski's rule of five violations, and toxicity were all factored into an ADMET research to determine their pharmacokinetic profile. The SWISSADME server was used to conduct the analysis of the ADMET characteristics. The pharmacokinetic, aqueous solubility, and pharmacodynamic aspects of the substances were evaluated using this web-based platform. Table 3 displays the expected pharmacological features, such as lipophilicity, drug similarity, water solubility, blood-brain barrier penetration, bioavailability score, and reactivity with cytochrome p450 isoforms.

Kaempferol, apigenin and quercetin all had excellent gastrointestinal (GI) absorption, as determined by pharmacokinetic study. These chemicals were also found to be unable to penetrate the brain's protective blood-brain barrier. These compounds did not demonstrate any deviation from the Lipinski rule of five, indicating that they are well suited for oral administration; they do not inhibit cytochrome P450, 2C9 or 2C19 but they do inhibit cytochrome P450, 1A2, 2D6, 3A4, and P-glycoprotein. The cytochrome P450 family of enzymes is well-known for its central role in the breakdown and elimination of several substances. Numerous studies have suggested that five isoforms of the superfamily (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) are substrates of around 50-90% of physiologically active substances, and reduction of the activity of these enzymes can elicit a drug-drug response. Both quercitrin and chlorogenic lack the ability to penetrate the blood-brain barrier and do not inhibit cytochrome P450 enzymes 1A2, 2C19, 2C9, 2D6, or 3A4. These chemicals have a low GI absorption but no toxicity toward the liver. Inhibition of P-glycoprotein is the only enzyme that rutin and hesperidin share in common; neither can pass the blood-brain barrier or affect cytochrome P450 enzymes 1A2, 2C19, 2D6, or 3A4. These chemicals have a low GI absorption rate yet do not have any harmful effects on the liver.

For a drug to be orally bioactive, it should not violate more than one of the following criteria: the molecular weight should be less than 500Da (MW500Da), the number of hydrogen bond donors should be less than 5, the number of hydrogen-bond acceptors should be less than 10, and the octanol-water partition coefficient should be less than 5 (log P5). Molecules that break two or more of these guidelines are ruled out as potential therapeutics [24].

As can be seen in the table above, our results reveal that Kaempferol, Apigenin and Quercetin all comply with Lipinski's rule of five, but chlorogenic acid has one infraction. Kaempferol, and apigenin and quercetin are all promising active oral medicines since they follow Lipinski's rule of five. These findings, together with those from other experimental and computational studies, highlight the importance of these chemicals as potential therapeutic candidates.

Drug candidates must have the lipophilicity to cross the lipid bilayer of most cell membranes, including those of enterocytes. Therefore, medication molecules need to be lipophilic in order to be absorbed effectively. The degree to which a chemical is lipophilic is typically quantified in terms of its LogP (the logarithm of the octanol-water partition coefficient), which is especially relevant for orally administered medications. Absorption is often low for logP values that are high, and vice versa for logP values that are low. According to Arnott and Planey [25] compounds with a logP value under 5 are more likely to be absorbed by the body. For the best trade-off between permeability and first-pass clearance, a value between 2 and 3 is typically recommended. Potential medication candidates must be adequately hydrophilic to allow their transport via the systemic circulation and so reach the cells where they are needed [26]. The logS value (solubility) is another measure of drug-likeness alongside the logP value. The number of 4 for logS is about right. However, the logS values of the vast majority of currently available medications fall within the range of -4 and -1.35. LogS values in that variety can be found for kaempferol, quercetin, and chlorogenic acid [27].

The Polar Surface Area (PSA) of a molecule is equal to the sum of the surfaces of its polar atoms. PSA is a great benchmark for measuring membrane permeability and the movement of molecules across them. Intestinal absorption, bioavailability, and blood-brain barrier penetration are just few of the things that PSA can predict for a particular medicine. For a molecule to be considered drug-like, its PSA must be less than 120 2 [28]. Only Rutin and Hesperidin have Topological Polar Surface Area (TPSA) values more than 200A among the substances tested here.

Table 3. ADMET profile of the hit compounds

Models	Kaempferol	Quercetin	Quercitrin	Apigenin	Chlorogenic acid	Rutin	Hesperidin
CYP1A2 inhibition	+	+	-	+	-	-	-
CYP2C19 inhibition	-	-	-	-	-	-	-
CYP2C9 inhibition	-	-	-	-	-	-	-
CYP2D6 inhibition	+	+	-	+	-	-	-
CYP3A4 inhibition	+	+	-	+	-	-	-
Gastrointestinal absorption	High	High	Low	High	Low	Low	Low
Blood Brain Barrier Permeation	-	-	-	-	-	-	-
P-glycoprotein substrate	-	-	-	-	-	+	+
Log K_p (skin permeation)	-6.70cm/s	-7.05cm/s	-8.42cm/s	-5.80cm/s	-8.76cm/s	-10.26cm/s	-10.12cm/s
Lipinski's rule	0	0	2	0	1	3	3
Log P value	1.7	1.63	1.6	1.89	0.87	1.58	2.6
Log S value	-3.86	-3.91	-4.44	-4.59	-2.58	-4.87	-4.33
TPSA	111.13	131.36	190.28	90.9	164.75	269.43	234.29
Molar mass	286.24	302.24	448.38	270.24	354.31	610.52	610.56
Hydrogen bond donors	4	5	7	3	6	10	8
Oral Bioavailability [H1]	0.55	0.55	0.17	0.55	0.17	0.11	0.17

Furthermore, most commercially accessible medicines have molecular weights below 500 g/mol. It has been demonstrated that heavier molecules have a lower probability of absorption and site-specific localization. All chemicals have molecular weights lower than 500 g/mol except for Rutin and Hesperidin.

Drug bioavailability after oral administration can be predicted by counting rotatable bonds. Oral bioavailability is predicted to be high for molecules containing 10 rotatable bonds or fewer, according to a number of studies. Rutin, hesperidin, and quercetin all have a bioavailability score of 0.17 and chlorogenic acid with a score of 0.11, which does not indicate good oral bioavailability based on Lipinski's rule, according to the pharmacokinetic screening of the compounds [29,30,26]. However, Kaempferol, Quercetin, and Apigenin all have scores of 0.55 on the Lipinski rule, indicating that they are suitably absorbable molecules when taken orally.

5. CONCLUSION

The present study looks at the inhibitory potential of *Nigella sativa*'s defined phytochemicals on the anti-apoptotic proteins Mcl-1 and Bcl-xl. When docked and compared with co-crystallized compounds that were crystallized with the standards, it can be concluded that seven compounds—apigenin, chlorogenic acid, hesperidin, quercetin, quercitrin, kaempferol, and rutin—may possess better inhibitory potential against the targets. The compounds' ADMET study found that they are mildly drug-like. More *in-silico*, in-vivo, and in-vitro experiments are needed to validate this experiment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021;71(3):209-249.
2. Gopal Krishnan PD, Golden E, Woodward EA, Pavlos NJ, Blancafort P. Rab GTPases: emerging oncogenes and tumor suppressive regulators for the editing of survival pathways in cancer. Cancers. 2020;12(2):259.
3. Gyamfi J, Kim J, Choi J. Cancer as a metabolic disorder. International Journal of Molecular Sciences. 2022;23(3):1155.
4. Khalil AM. Apoptosis, guardian of the genome. World Journal of Biology Pharmacy and Health Sciences. 2021; 5(1):037-054.
5. Morris JL, Gillet G, Prudent J, Popgeorgiev N. Bcl-2 family of proteins in the control of mitochondrial calcium signalling: an old chap with new roles. International Journal of Molecular Sciences. 2021;22(7):3730.
6. Obeng E. Apoptosis (programmed cell death) and its signals-A review. Brazilian Journal of Biology. 2020;81:1133-1143.
7. Neophytou CM, Trougakos IP, Erin N, Papageorgis P. Apoptosis deregulation and the development of cancer multi-drug resistance. Cancers. 2021;13(17): 4363.
8. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Turk B. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death & Differentiation. 2018;25(3):486-541. Available:https://doi.org/10.1038/s41418-017-0012-4.
9. Chota A, George BP, Abrahamse H. Interactions of Multidomain Pro-Apoptotic and Anti-Apoptotic Proteins in Cancer Cell Death. Oncotarget. 2021;12:1615–1626. DOI: 10.18632/oncotarget.28031.
10. Zhang X, Thummuri D, Liu X, Hu W, Zhang P, Khan S, Yuan Y, Zhou D, Zheng G. Discovery of PROTAC BCL-XL degraders as potent anticancer agents with low on-target platelet toxicity. European journal of medicinal chemistry. 2020;192:112186. Available:https://doi.org/10.1016/j.ejmech.2020.112186.
11. Shahar N, Larisch S. Inhibiting the inhibitors: Targeting anti-apoptotic proteins in cancer and therapy resistance. Drug resistance updates: reviews and commentaries in antimicrobial and anticancer chemotherapy. 2020;52: 100712. Available:https://doi.org/10.1016/j.drup.2020.100712
12. Stevens M, Oltean S. Modulation of the apoptosis gene Bcl-x function through

alternative splicing. Frontiers in Genetics. 2019;10:804.

13. Di Cristofano FR, Fong MW, Huntington KE, Carneiro BA, Zhou L, El-Deiry WS. Synergistic activity of ABT-263 and ONC201/TIC10 against solid tumor cell lines is associated with suppression of anti-apoptotic Mcl-1, BAG3, pAkt, and upregulation of pro-apoptotic Noxa and Bax cleavage during apoptosis. American Journal of Cancer Research. 2023;13 (1):307.
14. Xiang W, Yang CY, Bai L. MCL-1 inhibition in cancer treatment. OncoTargets and therapy. 2018;11:7301–7314.
Available:https://doi.org/10.2147/OTT.S146228Karacil, 2022
15. Bolomsky A, Vogler M, Köse MC, Heckman CA, Ehx G, Ludwig H, Caers J. MCL-1 inhibitors, fast-lane development of a new class of anti-cancer agents. Journal of hematology & oncology. 2020;13: 1-19.
Available:https://doi.org/10.1186/s13045-020-01007-9
16. Chin HS, Fu NY. Physiological functions of Mcl-1: insights from genetic mouse models. Frontiers in cell and developmental biology. 2021;9:704547.
17. Senichkin VV, Streletskaia AY, Gorbunova AS, Zhivotovsky B, Kopeina GS. Saga of Mcl-1: regulation from transcription to degradation. Cell Death & Differentiation. 2020;27(2):405-419.
18. Mofio BM, Okwute SK, Abdullahi GL. Biological and chemical evaluations of the seeds of Nigella sativa Linn (Ranunculaceae). Journal of Pharmacognosy and Phytochemistry. 2020;9(4):3452-3457.
19. Salih HM, Aljabre, Omar M, Alakloby, Mohammad A. Randhawa Dermatological effects of Nigella sativa. Journal of Dermatology & Dermatologic Surgery. 2015;19(2):92-98.
Available:https://doi.org/10.1016/j.jdds.2015.04.002.
20. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports. 2017; 7(1):42717.
21. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic acids research. 2018;46(W1):W257-W263.
22. Bououden W, Benguerba Y. Computational quantum chemical study, drug-likeness and in silico cytotoxicity evaluation of some steroidal anti-inflammatory drugs. Journal of Drug Delivery and Therapeutics. 2020;10(3-s):68-74.
23. Şahin İ, Çeşme M, Özgeriş FB, Güngör Ö, Tümer F. Design and synthesis of 1, 4-disubstituted 1, 2, 3-triazoles: Biological evaluation, in silico molecular docking and ADME screening. Journal of Molecular Structure. 2022;1247:131344.
24. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews. 2012; 64(SUPPL.):4–17.
Available:https://doi.org/10.1016/j.addr.2012.09.019
25. Arnott JA, Planey SL. The influence of lipophilicity in drug discovery and design. Expert opinion on drug discovery. 2012;7 (10):863-875.
26. Akinnusi PA, Olubode SO, Alade AA, Ashimi AA, Onawola OL, Agbolade AO, Adeniran OY. Potential Inhibitory Biomolecular Interactions of Natural Compounds with Different Molecular Targets of Diabetes. Bioinformatics and Biology Insights. 2023;17: 11779322231167970.
27. Kolodziejczyk-Czepas J, Ponczek M, Sady-Janczak M, Pilarski R, Bukowska B. Extracts from Uncaria tomentosa as antiplatelet agents and thrombin inhibitors–the in vitro and in silico study. Journal of Ethnopharmacology. 2021;267:113494.
28. Soliman ME, Adewumi AT, Akawa OB, Subair TI, Okunlola FO, Akinsuku OE, Khan S. Simulation models for prediction of bioavailability of medicinal drugs—the interface between experiment and computation. AAPS PharmSciTech. 2022; 23(3):86.
29. Mahanthesh MT, Ranjith D, Yaligar R, Jyothi R, Narappa G, Ravi MV. Swiss ADME prediction of phytochemicals present in Butea monosperma (Lam.) Taub. Journal of Pharmacognosy and Phytochemistry. 2020;9(3):1799-1809.

30. Sravika N, Priya S, Divya N, Jyotsna PMS, Anusha P, Kudumula N, Bai SA. Swiss ADME properties screening of the phytochemical compounds present in Bauhinia acuminata. Journal of Pharmacognosy and Phytochemistry. 2021;10(4):411-419.

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