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Research Article

In-silico investigation of alpha-bisabolol and derivatives as inhibitors of bcl-2 family proteins for targeting glioblastoma

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Abstract: Glioblastoma is one of the most common and destructive types of tumors, with an increasing number around the world. Alpha-bisabolol is a plant secondary metabolite with discovered anticancer activity, which can also be considered a potential treatment for glioblastoma. *In silico* investigations can provide adequate information for understanding the roles of alpha-bisabolol compounds in glioblastoma. For this purpose, computational drug design procedures were applied to investigate the anti-glioblastoma biotherapeutic potential of alpha-bisabolol compounds. In this study, bcl-2 family proteins' inhibitory activity of alpha-bisabolol compounds and their toxicity properties were investigated by molecular docking studies. Toxicity properties were evaluated by the prediction tools as, CarcinoPred for carcinogenicity and LAZAR for mutagenicity, pkCSM, and SwissADME for absorption, distribution, metabolism, excretion and toxicity (ADMET) analysis and BOILED-Egg model, PASS prediction to analyze biological functions and druggability, DruLiTo program to compute the drug likeness property and QSAR Toolbox for QSAR modeling. The results reveal the potential of alpha-bisabolol oxide B, a plant secondary metabolite and an alpha bisabolol derivative, in glioblastoma for the inhibitory mechanisms of bcl-2 family proteins, being non-toxic and non-mutagenic.

1. INTRODUCTION

Brain tumors have recently become a trending topic for researchers because of their negative impact on neurological functions and physiological behaviors with poor diagnosis and treatment. Approximately 60% of all brain tumors are gliomas, which are rapidly progressive malignant brain tumors driven by glial activity (Hanif *et al*., 2017). Today, treatment strategies are limited in this tumor group, as in other types of cancer, and investigation of high-efficiency chemotherapeutic drug molecules for glioma is essential for increasing the quality of life of patients and their life span with accurate treatment strategies (Davis, 2016). When radiotherapy, chemotherapy, and surgical treatment strategies are combined with late diagnosis and awareness processes, the applicability and effectiveness of these treatments decrease (Al-Azri, 2016). Therefore, the discovery of direct-to-target innovative drug agents is an essential preliminary step in controlled drug delivery studies. There are numerous natural substances

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originating from plants that have anticancer properties (Gielecińska *et al*., 2023). One of the most common anticancer drug compounds is paclitaxel, also known as taxol, derived from *Taxus brevifolia* Nutt. (Lim *et al*., 2022). This compound is actively used in first-line treatments for various other cancers, including ovarian carcinoma and breast cancer (Mosca *et al*., 2021). Another phytochemical alkaloid compound is oncovin, also known as vincristine, which is derived from *Vinca rosea* L. and has great potential for treating acute leukemia and malignant lymphoma (Škubník *et al*., 2021). Terpenes and their derivatives are large, diverse phytochemical compounds with great potential for biotherapeutic effects such as antimicrobial, anti-inflammatory, antioxidant, and anticancer (Kamran *et al*., 2022). The impact of terpenes on different cancer types also has been studied both in vitro and in vivo (Tomko *et al*., 2020). One of the sesquiterpenoid, alpha bisabolol, is mostly found in aromatic floral plants with anti-inflammatory, skin-soothing, wound healing, nephroprotective, and anticancer biotherapeutic features (Eddin *et al*., 2022; Ramazani *et al*., 2022). Alpha bisabolol tends to oxidize; therefore, the most common derivatives are alpha bisabolol oxides A and B (Detoni *et al*., 2009). Although many researchers have focused on the anticancer activities (such as pancreatic, endometrial and lung cancer) of bisabolol and its derivatives, *in silico* drug design against glioma based on these compounds has not been investigated (Murata *et al*., 2017; Fang *et al*., 2019). The main step in the *in silico* anticancer drug design was to determine how the phytochemical agent acts. Specification of cancer and related signaling pathways is important for the specification of targeted biological structures. Evading apoptosis and uncontrolled proliferation are characteristic features of cancer cells; hence, anticancer drug development strategies mostly focus on the apoptotic pathway and related protein structures (Pfeffer & Singh, 2018). For glioma, bcl-2 family proteins play key roles with upregulation and downregulation during the apoptosis and influencing the degree (Kale *et al*., 2018). This family proteins include bcl-xl, bcl-2, bcl-w, and mcl-1. In this study, the aim was to reveal the biotherapeutic potential of bioactive compounds that may exhibit anti-apoptotic effects against glioblastoma and to evaluate them within the context of glioblastoma. For this purpose, alpha bisabolol and its oxide derivatives were analyzed using *in silico* methods. Carcinogenicity and mutagenicity were predicted. Then, drug similarity and PASS properties were computationally observed using web-based tools. QSAR models for alpha bisabolol and oxides A and B were created, and their ligand structures were analyzed in detail. Subsequently, molecular docking experiments for bcl-2 family target proteins were performed, and chemical bond interactions were observed at the molecular level. The ADMET properties of the alpha bisabolol, oxide A, and oxide B structures were estimated separately, and their drug features were predicted.

The results obtained after the analysis indicate that the bcl-2 family proteins can be inhibited by alpha-bisabolol and its derivatives, showing high binding affinity. Specifically, it has been demonstrated that alpha-bisabolol oxide B holds great potential against glioblastoma in this context.

2. MATERIAL and METHODS

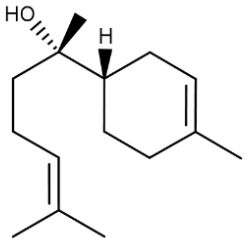
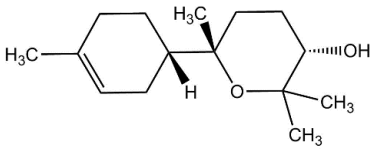
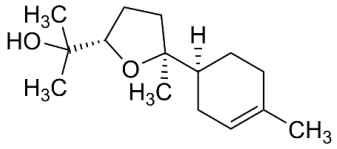
2.1. Dataset Sources

The main source of alpha-bisabolol and its derivatives as secondary metabolites is plants. Some of these plants and the research studies from which they were obtained are presented in Table 1.

2.2. Glioblastoma Target Protein-Protein Interaction (PPI) Analysis

The interactions among bcl-2 family proteins responsible for modulating apoptosis in glioblastoma were analyzed using the STRING online web tool (Szklarczyk *et al*., 2015). Initially, the protein names were entered sequentially into the multiple protein tab, and suitable structures were selected. Then the interaction score was set to high confidence (0.7) and all active interaction sources were examined.

Table 1. Aromatic plants containing alpha bisabolol and its derivative as an active ingredient.

Compound	Chemical Structure	Plant Sources
Alpha bisabolol		• *Lavandula angustifolia* (Mantovani *et al*., 2013) • *Hypericum perforatum* (Morshedloo *et al*., 2015) • *Rosmarinus officinalis* (Tawfeeq *et al*., 2016) • *Artemisia absinthium* (Rizvi *et al*., 2018)
Alpha bisabolol oxide A		• *Thymus vulgaris,* and *Salvia officinalis* (Kowalski *et al*., 2009) • *Achillea millefolium* (Costescu *et al*., 2014)
Alpha bisabolol oxide B		• *Mentha piperita*, *Thymus vulgaris* and *Salvia officinalis* (Kowalski *et al*., 2009) • *Achillea millefolium* (Costescu *et al*., 2014)

2.3. Molecular Docking

Structures of bcl-2 (PDB:2W3L), bcl-xl (PDB: 3ZK6), bcl-w (PDB: 2Y6W), and mcl-1 (PCB: 6OQC) were retrieved from the Protein Data Bank (PDB). Each protein structure was used as a receptor and remained rigid. For the docking preparation procedure of proteins, the following steps were applied: (i) energy minimization was performed with 100 steepest descent steps with a 0.02 Å step size and an update interval of 10, (ii) water molecules were removed, (iii) solvent and non-complex ions were deleted, and (iv) polar hydrogen atom and AM1-BCC charges were added (Jakalian *et al*., 2002). For ligand structure retrieval and preparation, alpha bisabolol, oxide A, and B structures were downloaded from the PubChem database in .sdf format. These three phytochemicals were prepared similarly to the protein preparation steps, but charge addition was based on the Gasteiger charge model (Gasteiger & Marsili, 1978). To determine phytochemicals and apoptotic proteins target interactions at the molecular level, semi-flexible molecular docking simulations were performed by using AutoDock Vina. First, the blind docking method was implemented to investigate the binding sites of the protein, and the results were compared with those reported in the literature (Poustforoosh *et al*., 2022). Then, oriented docking was performed with specified coordinates, and the top 2 minimum binding energy poses of each protein were visualized with Discovery Studio Visualizer (Biovia, 2021).

2.4. Mutagenicity Prediction

The AMES test, also known as the bacterial reverse mutation assay, is a common method used to determine the mutagenic properties of various chemical substances. Lazar, a web-based computational tool helps in the prediction of complicated toxicological outcomes such as toxicity, carcinogenicity, and blood brain barrier (BBB) permeation (Helma *et al*., 2017). Lazar employs data mining algorithms to input experimental data and generate predictions for unknown chemical ligands.

2.5. Carcinogenicity Prediction

The potential of any chemical to induce carcinogenicity in humans and animals can be predicted computationally using Carcinogenicity Prediction using Ensembled Learning Methods (CarcinoPred-EL). This prediction algorithm is created by combining different programs (RF, SVM and XGBoost), resulting in values with high sensitivity, accuracy, and specificity rates

(Zhang *et al*., 2017). The relevant prediction program compares the data entered in SMILES format with the chemicals in its database and provides an average carcinogenicity result. The program's algorithm conducts this by analyzing the functional groups and main skeleton similarities of the chemicals.

2.6. PASS Prediction

The PASS (Prediction of Activity Spectra for Substances) online web tool enables prediction of the expected biological function profile of a chemical compound with similarities to a drug. Computational predictions can be obtained by inserting chemical SMILES code of the chemical structures. The PASS tool prediction results 2 category labels of "probability to be active" (Pa) or "probability to be inactive" (Pi) as biological activity (Filimonov *et al*., 2014)

2.7. Drug-likeness Prediction

Drug-likeness prediction of alpha-bisabolol and its derivatives was predicted using the drug-likeness tool (DruLiTo) software. The chemical structure of the bioactive compounds was inputted into the software in the form of Structure -Data Files (.sdf) file format. To investigate druggability properties, three filters were applied which are Lipinski's rule, Veber filter, and Ghose filter (Bickerton *et al*., 2012).

2.8. Toxicity Prediction (Pimephales promelas) by QSAR Modeling

QSAR activity analyses were performed using the QSAR Activity Toolbox Version 4.6 package program. After the relevant parameters were estimated for the phytochemicals, the standard QSAR activity calculation path was followed which included selection of the true chemical structures, categorization, and gathering the data for model building (Mombelli *et al*., 2021). Adhering to the standard algorithm of the program, "Fish, LC50 (EC50) at 96h for *P. promelas* effect Mortality" was implemented via an automated workflow (Yordanova *et al*., 2019). This program is a system that performs predictions through a mathematical model based on processed data. The QSAR model for the processed data is trained to predict the 96-hour LC50 (EC50) values for *P. promelas* and defines the relationship between chemical structural properties and mortality. Subsequently, the study standardizes the physicochemical and topological properties of the entered chemicals and makes predictions by defining a mathematical equation related to the actual values.

2.9. ADME/T Analysis

ADME/T (absorption, distribution, metabolism, excretion, and toxicity) analysis was performed as the last step of the *in silico* experiments. The SwissADME (Daina *et al*., 2017) and pkCSM (Pires *et al*., 2015) web tools and literature data were used for these predictions. For analysis, the SMILES chemical data format of all three bioactive compounds was retrieved from the PubChem database.

2.10. Predicting Gastrointestinal Absorption and Brain Penetration

The two primary pharmacokinetic parameters crucial for assessing the bioactive substance's absorption in the gastrointestinal tract and its permeability into the brain can be estimated through the Brain or Intestinal Estimated Permeation (BOILED-Egg) computational *in silico* prediction model. This model evaluates the lipophilicity and polarity of the molecule entered, producing results accompanied by easily understandable graphical representations (Daina & Zoete, 2016).

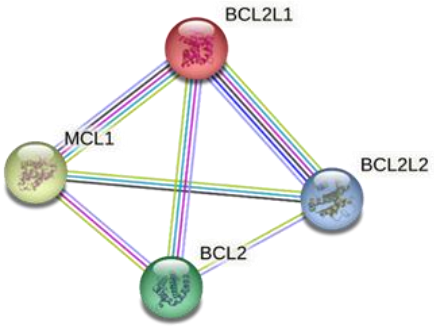
3. RESULTS and DISCUSSION

3.1. PPI Analysis of bcl-2 Family Proteins

The interactions among the proteins of the bcl-2 family are presented in Figure 1. The colors of interactions between proteins are represented in different colors: purple indicates experimentally determined interactions, blue indicates interactions from curated databases,

green indicates gene neighborhood, red indicates gene fusion, navy blue indicates gene co-occurrence, yellow indicates data mining, and gray indicates protein homology.

Figure 1. bcl-2 family proteins PPI (BCL2L1: bcl-xl and BCL2L2: bcl-w).



The consistency of the conducted PPI analysis with literature data has been determined (Calis *et al*., 2022; He *et al*., 2022). As seen in the Figure, proteins interact with each other in multiple ways, suggesting their involvement together in the regulation of disrupted apoptotic processes during cancer.

3.2. Molecular Docking

The analyses were conducted using AutoDock Vina, with UCSF Chimera utilized as the interface program. The binding affinity values obtained from the ligand-protein binding analyses were selected from RMSD 0 groups and ranked accordingly. Binding affinities are calculated by the AutoDock Vina algorithms based on Gibbs free energy (ΔG); the more negative the energy, the stronger affinity and binding. The molecular docking results are given in Table 2.

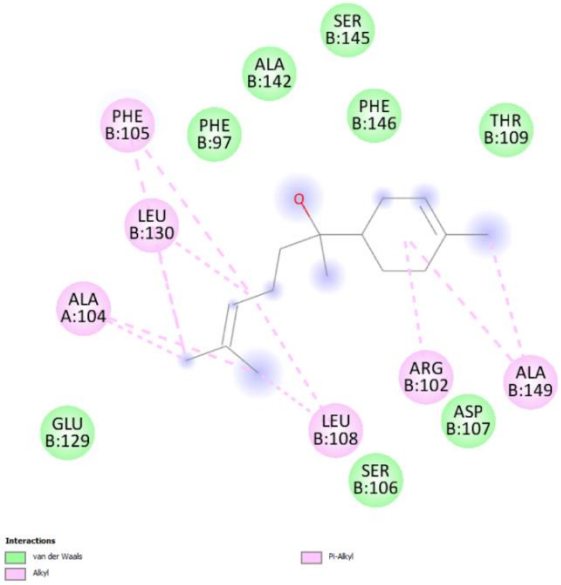
Table 2. Molecular docking scores and hydrogen bond interactions.

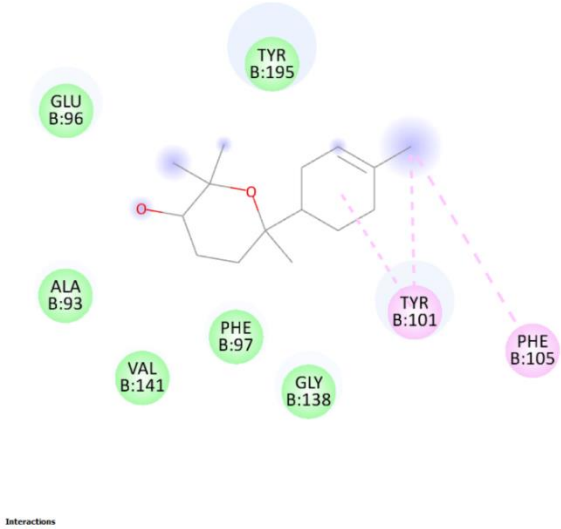
	Binding Affinities (kcal/mol)				Hydrogen Bond Residues			
Compounds	bcl-2	bcl-xl	bcl-w	mcl-1	bcl-2	bcl-xl	bcl-w	mcl-1
Alpha Bisabolol (AB)	-5.7	-8.1	-7	-7.5	-	-	-	-
AB Oxide A	-6.6	-7.9	-7.2	-7.9	SER75	-	ALA98 PHE 102	-
AB Oxide B	-6.5	-8.5	-7.2	-7.3	ARG26	ARG100 ALA104	PHE57	-

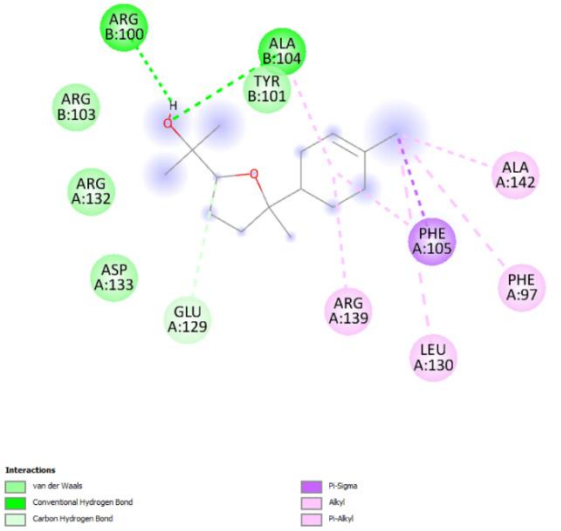
As noticed in Table 2, the highest interaction scores were determined on the bcl-xl protein, while the lowest interaction was observed against the bcl-2 protein. According to a glioblastoma study with the same method, the bcl-xl target was determined as the most effective and potential target, as found in our results (Poustforoosh *et al*., 2022). The 2D illustration of molecular docking targeting the bcl-xl receptor is provided in Figure 2.

Alpha bisabolol oxide B exhibited the highest activity and was determined to be the compound most tended to create hydrogen bonding. This indicates the inhibitor behavior strength of the bioactive component towards the target and its anticancer potential as well. Alpha bisabolol demonstrated a tendency to create alkyl bond interactions, forming a high number of alkyl bonds with all members of the bcl-2 family proteins. However, the binding score of alpha-bisabolol oxide A remained lower compared to the other two bioactive compounds, resulting in a relatively lower number of Van der Waals interactions and alkyl bonds. Common alkyl bonds were found in the residues PHE105 and LEU130, while a Van der Waals interaction was observed in the PHE97 residue.

Figure 2. Interaction of (a) alpha bisabolol, (b) alpha bisabolol oxide A, (c) alpha bisabolol oxide B with bcl-xl.







The reference study of the protein identified a hydrophobic pocket, which includes the PHE105 residue, where alkyl bonds are formed within hydrophobic regions (Lessene *et al*., 2013). The blue circular shapes surrounding some ligand points represent the intensity of interaction attraction from a pharmacophore perspective (Biovia, 2021). There is a significant intensity of interaction attraction at different binding sites of the ligand, especially for alpha bisabolol oxide B. The inhibition of the bcl-xl protein in the reference study also focused on anticancer strategies (Lessene *et al*., 2013), and when the molecular docking strategy employed in our study was applied, the obtained binding affinity value was found to be -12.3 kcal/mol. Comparing our determined binding affinity value of -8.5 kcal/mol with the reference value, reveals a considerably high inhibitor interaction.

Our bcl-2 family protein inhibitor results are also consistent with studies conducted in the literature. In an *in vivo* anti-apoptotic study conducted against testicular toxicity in rats, alpha-bisabolol provided overall anti-inflammatory activity by activating Nrf2 antioxidant activity and reducing NF-κB / MAPK signal activation (Arunachalam *et al*., 2022). In another study, it was determined that oral consumption of alpha-bisabolol reduced neurodegeneration in Parkinson's disease by decreasing oxidative stress, neuroinflammation, and apoptosis (Javed *et al*., 2020)

3.3. Mutagenicity and Carcinogenicity Predictions

The computational analysis results regarding the probability of alpha bisabolol and its derivatives being mutagenic and carcinogenic are presented in Table 3. The average values calculated using the RF method for highly carcinogenic compounds are close to 1, whereas the values obtained for alpha-bisabolol, and its derivatives remain below the average carcinogenicity (0.5) (Helma, 2006). These bioactive compounds, currently utilized in the pharmaceutical and cosmetic industries, as evident from the results, do not possess carcinogenic or mutagenic effects at moderate concentrations (Eddin *et al*., 2022).

Table 3. Carcinogenicity and mutagenicity prediction results.

Compound Name	CarcinoPred -EL Method	Average	Predicted Result	Mutagenicity Prediction
Alpha Bisabolol (AB)	RF	0.31	Non-carcinogen	Non-mutagenic
AB Oxide A	RF	0.29	Non-carcinogen	Non-mutagenic
AB Oxide B	RF	0.34	Non-carcinogen	Non-mutagenic

3.4. PASS Prediction Results

In this study, analysis of the possibilities of alpha-bisabolol and derivatives activity through the PASS online tool revealed that all 3 molecules were drug-like with CYP2J substrate (Pa>0.7 and Pi>0.01) and antimetastatic (Pa>0.6 and Pi:0.04) and other activities are given in Table 4. It is known that Pa values above 60% indicate strong similarity, as known from previous studies. Consistently with our other *in silico* analyses, the highest antimetastatic effect was found in alpha-bisabolol oxide B. Surprisingly, alpha bisabolol exhibited a significantly higher apoptosis agonist effect compared to the other two compounds. The high antitumor property of alpha-bisabolol oxide B is further supported by its antineoplastic (lung cancer) drug similarity, which was also the highest with a Pa of 0.798. Considering that the PASS analysis values reported in the literature for flavonoid trimethoxyflavone are Pa > 70% (Pires *et al*., 2015) and for apigenin are Pa > 90% (Divya Rajaselvi *et al*., 2023), it can be inferred from the obtained drug similarity values that alpha bisabolol has high druggability potential.

In molecular docking studies, alpha bisabolol oxide B shows the highest affinity; however, the higher potential of alpha bisabolol against various diseases, as indicated by PASS analysis, can be attributed to its specificity. Alpha bisabolol oxide B is a derivative bioactive compound that has shown activity against apoptosis markers studied in this work, while alpha bisabolol

presents a broad spectrum of biotherapeutic potential. Additionally, literature indicates that alpha-bisabolol exhibits antiviral, anti-inflammatory, and immunosuppressant effects, as demonstrated through *in vitro* and *in vivo* studies (Sun *et al*., 2017; Al-Ghanim *et al*., 2023).

Table 4. PASS predictions.

	Alpha Bisabolol		AB Oxide A		AB Oxide B	
Activity	Pa	Pi	Pa	Pi	Pa	Pi
Apoptosis agonist	0.847	0.005	0.434	0.058	0.342	0.102
Anti-eczematic	0.830	0.013	0.749	0.031	0.709	0.043
CYP2J substrate	0.807	0.019	0.818	0.017	0.719	0.044
Retinol dehydrogenase inhibitor	0.763	0.002	0.399	0.012	0.359	0.016
Immunosuppressant	0.736	0.013	0.347	0.087	0.690	0.018
BRAF expression inhibitor	0.731	0.003	0.198	0.040	0.266	0.026
Antithrombotic	0.727	0.006	0.230	0.167	0.270	0.124
Antiviral (Rhinovirus)	0.664	0.004	0.412	0.079	0.414	0.077
Chemo-preventive	0.660	0.008	0.302	0.036	0.270	0.043
Carminative	0.678	0.008	0.556	0.014	0.316	0.042
Antineoplastic	0.657	0.034	0.374	0.027	0.798	0.012
Anti-inflammatory	0.652	0.022	0.241	0.199	0.388	0.102
Antimetastatic	0.638	0.004	0.617	0.004	0.639	0.004

Lipinski's Rule of Five is specifically designed to illustrate a compound's oral bioavailability and assists in evaluating its absorption and penetration into lipid bilayers. According to this rule, a compound should not exceed certain thresholds: a molecular weight limit of 500 Da, no more than five hydrogen bond donors, a log P value of no more than five, and fewer than five hydrogen bond acceptors (Lipinski *et al*., 1997). Table 5 obtained from DruLiTo software indicates that alpha-bisabolol and its derivatives satisfy the Lipinski, Veber, and Ghosh rules. It has been predicted that the molecular weights (MW) of all three molecules are greater than 220 g/mol, with log P values of 4.085 for alpha-bisabolol and 3.176 for both alpha-bisabolol oxide A and B with at least 1 H donor and acceptor atoms. The total polar surface area (TPSA) refers to the cumulative surface area occupied by all polar atoms, including nitrogen, hydrogen, and oxygen, within a molecule. This measurement indicates a molecule's ability to penetrate biological barriers such as the blood-brain barrier (BBB). The TPSA values obtained from the analysis, around 20 $Å^2$, indicate blood-brain barrier (BBB) permeability (Prasanna & Doerksen, 2009). Although the TPSA values of secondary metabolites vary depending on the molecular structure, values obtained for standard bioactive compounds such as limonin, quercetin, and kaempferol derived from different plant species are typically around 100 $Å^2$, as reported in the literature (Oner *et al*., 2023).

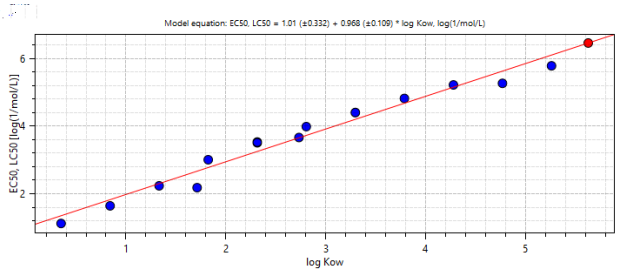
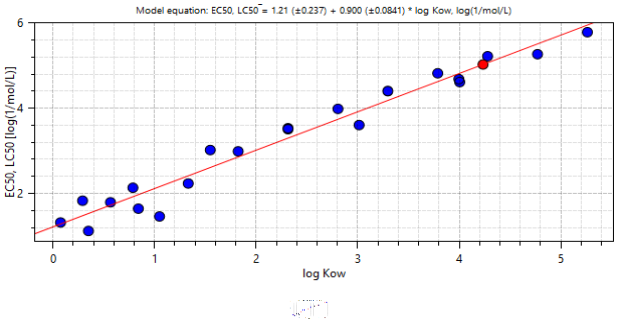
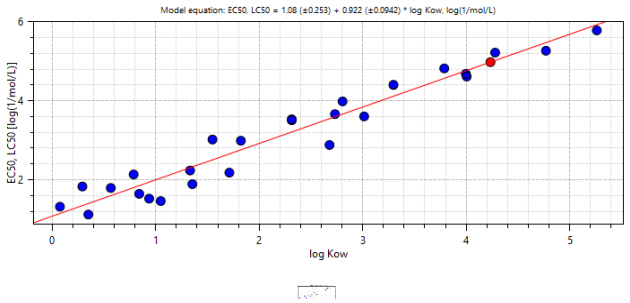
Table 5. Druglikeness assessment with DruLiTo program.

Compound	MW (g/mol)	logP	HBA	HBD	TPSA	Lipinski's rule	Ghose filter	Verber filter
Alpha Bisabolol (AB)	222.2	4.085	1	1	20.23	-	-	-
AB Oxide A	238.19	3.176	2	1	29.46	-	-	-
AB Oxide B	238.19	3.176	2	1	29.46	-	-	-

3.5. QSAR Analysis

In Table 6, the correlation between the LogLC50 value and the log-Kow value of alpha-bisabolol and its derivatives, which affect the organism used *in silico* experiments, is shown. As observed, there is a positive correlation between the log-Kow value and the LogLC50 value, with a simultaneous increase observed. An increase in the LogLC50 value indicates a decrease in toxicity, and this phenomenon resulted in similar observations on the organism for all three compounds (Ha *et al.*, 2019). On the other hand, when comparing the obtained LC50 values with the toxicity report of bisabolol, it can be said that the values are close to the average toxicity limit (Andersen, 1999). Considering that the toxicity value for ibuprofen, commonly used in comparative toxicity studies, is 3 mg/l, the values obtained for alpha bisabolol oxide A and B, which are 2.24 and 2.5 mg/l respectively are in the average toxicity range (Wade *et al.*, 1997). Other important QSAR result values are R^2 and Q^2, which means the optimistic evaluation of model fit and consistency lacks a proper standard of comparison. R^2 value generally gives a model fit to the original data measurement, and Q^2 gives a measurement of consistency between the original and predicted data (Worley & Powers, 2013). Both values can be a maximum of 1, in which case the obtained measurement values from QSAR analysis are quite high.

Table 6. Computational QSAR models for alpha bisabolol and derivatives.

No	Name	Model	LC_{50}	R^2	Q^2
1	Alpha bisabolol		0.0773 mg/l	0.978	0.971
2	Alpha bisabolol oxide A		2.24 mg/l	0.953	0.943
3	Alpha bisabolol oxide B		2.5 mg/l	0.942	0.940

3.6. ADMET Prediction

Estimation of various ADMET properties of alpha-bisabolol and its derivatives are given in Table 7. For an average ADMET property, the molecular weight of the phytochemicals should be in the range of 180–480 Da (see Table 5). Because heavy molecules will take longer to be absorbed and their mechanism of action is unclear, it is mostly expected that drug molecules will be as light as possible. Similarly, because of the prediction that heavy atoms will be difficult to pass through membranes and the toxicity profile will increase, it is expected that drug molecules will not contain as many heavy atoms as possible (<36) (Zhong *et al*., 2013). The Csp3 fraction affects the metabolic stability of the drug formula and molecules with a high sp3 hybridization value are more stable than molecules of the sp2 hybridization fraction. The Csp3 value is mostly expected to be around 0.6 (Cervelli & Russ, 2010). On the other hand, the lipophilicity of the drug directly affects its distribution in the body, drug metabolism, and biocompatibility. In drug development studies conducted for a lipid-rich tissue target, drug lipophilicity is expected to be quite high. Because the target mechanism mentioned in this study is the brain and surroundings, it is expected that the phytochemicals examined by the presence of adipose tissue will have high lipophilicity (1-3). Like lipophilicity, solubility should be high for better distribution, bioavailability, and absorption. For the glioma study, alpha-bisabolol and its derivatives are expected to be soluble (Chandrasekaran *et al*., 2018).

Most cancer drugs are administered orally for patient comfort and ease of use. Therefore, GI absorption is critical for determining the bioavailability of these drugs. Enough of the drug must reach the systemic circulation to achieve effective absorption. Therefore, for effective glioma-targeted drug development, drug molecules should also pass through the blood-brain barrier (BBB) (Chandrasekaran *et al*., 2018).

Table 7. ADMET prediction.

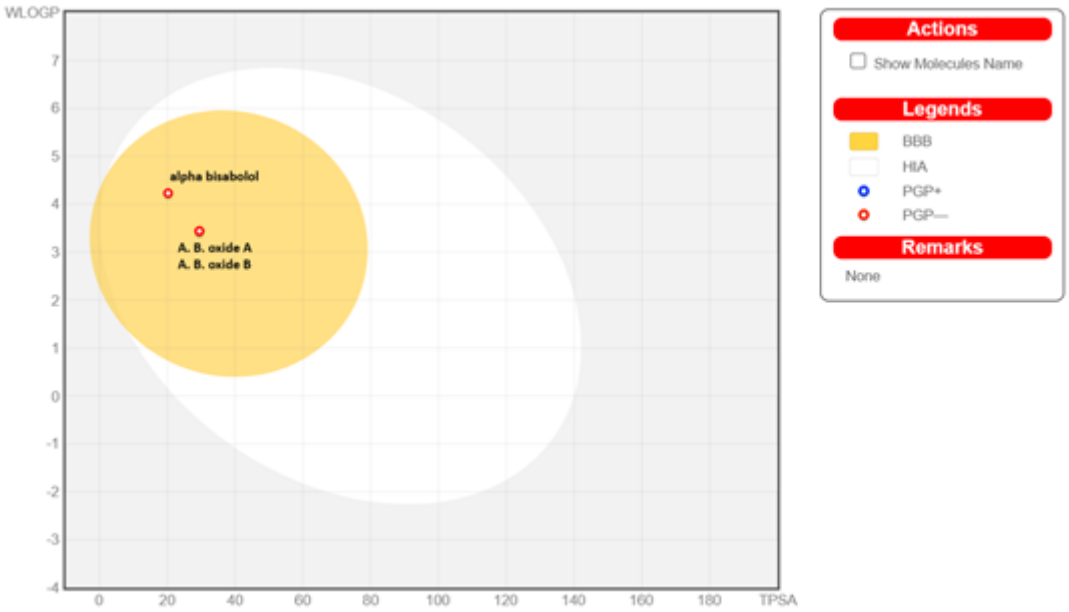
Predicted Model	Alpha Bisabolol	AB Oxide A	AB Oxide B
Water solubility (Log mol/L)	-4.379	-3.41	-3.396
Fraction Csp3	0.321	0.45	0.481
Caco2 permeability (Log Papp in 10^{-6} cm/s)	1.505	1.607	1.605
Intestinal (GI) absorption (%)	93.014	93.989	93.958
Skin permeability (log Kp)	-1.761	-2.919	-2.912
P-glycoprotein substrate	No	No	No
P-glycoprotein inhibitor	No	No	No
BBB permeability (log)	0.605	0.514	0.533
Total clearance (log ml/min/kg)	1.363	1.115	1.117
CYP3A4 inhibitor	No	No	No
CYP2C19 inhibitor	Yes	No	No
Hepatotoxicity	No	No	No

3.7. BOILED-EGG Model

The BOILED-Egg model predictions for alpha-bisabolol and its derivatives are presented in Figure 3. Due to their structural similarities, alpha-bisabolol oxide A and B are localized in the same region of the model. Additionally, also all three compounds are situated in the yolk region of the egg. From these observations, it can be inferred that all three compounds exhibit hydrophilic properties, have BBB permeability, and may have relatively slow cellular permeability due to P-glycoprotein (PGP-) substrates inhibition.All three bioactive components investigated in the study have shown BBB permeability, which indicates the potential for direct access to brain tissue and more effective intervention with tumor cells, reflecting high efficacy and bioavailability. Another advantage of these components crossing the BBB is the possibility

of using them in combination with other treatment methods (e.g., radiotherapy or surgery). Figure 3 shows that alpha bisabolol exhibits higher permeability compared to the other two components, which is quite normal considering their molecular weights and sizes.

Figure 3. Prediction of GI absorption and BBB permeation by BOILED-EGG model.



4. CONCLUSION

The immediate need to screen, discover, and develop novel potential anticancer drugs with optimal therapeutic efficacy and minimal adverse effects is crucial in today's pharmacological topic. Apart from conventional in vitro models, computer-assisted algorithms or *in silico* modeling and prediction tools emerge as highly useful resources in the available array of alternative approaches. The toxicological attributes of a compound can be promptly and efficiently assessed through computerized methodologies. This study, based on various *in silico* prediction methods, demonstrates that alpha bisabol and oxidized products (alpha bisabolol oxide A and B) exhibit favorable drug-like properties without any evidence of carcinogenicity or mutagenicity. The research evaluates the anticancer activity of the alpha-bisabolol and derivatives targeting bcl-2 family proteins. The results indicate that alpha bisabolol oxide B exhibits high inhibitory activity at the molecular level with a binding affinity score of -8.5 kcal/mol. According to QSAR analysis results, the components do not show toxic effects and have high BBB permeability. They not only have anti-apoptotic effects against glioblastoma but also possess high biotherapeutic potential against various diseases, as evidenced by PASS analysis results. Further *in vitro* and *in vivo* validations are necessary to investigate their safety profile and potential interactions with other drugs.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Nilüfer Vural: Methodology, Supervision, Writing and Validation. **Sibel Kaymak**: Investigation, Visualization, Software, Formal Analysis, and Writing-original draft.

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