DOI: https://doi.org/10.54393/fbt.v4i02.105

FUTURISTIC BIOTECHNOLOGY

https://fbtjournal.com/index.php/fbt
ISSN (E): 2959-0981, (P): 2959-0973
Volume 4, Issue 2 (April-June 2024)

Original Article

OPEN ACCESS

Molecular Docking-Aided Identification of Natural Bioactive Molecules as Potential Cancer Cell Proliferation Inhibitors

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ARTICLE INFO

Keywords:
Cell Proliferation Inhibitors, Sesquiterpene Lactones, Molecular Docking

How to Cite:
Hassan, I., Gul, Sameena, Zaman, A., Zafar, E., & Khan, M. (2024). Molecular Docking-Aided Identification of Natural Bioactive Molecules as Potential Cancer Cell Proliferation Inhibitors: Molecular Docking as Cancer Cell Inhibitors. Futuristic Biotechnology, 4(02). https://doi.org/10.54393/fbt.v4i02.105

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Received Date: 9th February, 2024
Acceptance Date: 16th May, 2024
Published Date: 30th June, 2024

ABSTRACT

Cancer is the second leading cause of death worldwide. Uncontrolled proliferation of cells is a hallmark of cancer development and progression. Ki-67 (a marker of proliferation Kiel-67) and proliferating cell nuclear antigen (PCNA) are two major proliferations, diagnostic and prognostic biomarkers as these are over expressed in cancerous cells. Pharmacological inhibition of Ki-67 and PCNA could effectively inhibit the growth of cancer cells. **Objective:** To identify Sesquiterpene Lactones (SLs) as potential inhibitors of Ki-67 and PCNA to reduce cancer burden. **Methods:** The inhibitory potential of SLs, namely sulfocostunolide A, sulfocostunolide B, ilicol, eucalyptone, and ascleposide E were investigated using Molecular Docking (MD) analysis. MD analysis and visualization of ligand-protein complexes were performed using softwares such as MGL tools, BIOVIA Discovery Studio visualizer and LigPlot plus. Additionally, drug likeness and pharmacokinetic properties of SLs were assessed via pkCSM and ADMET analysis. **Results:** Results showed that eucalyptone with binding energy of -8.1 kcal/mol with Ki-67 while sulfocostunolide B with -6.4 kcal/mol binding energy with PCNA are the most potent proliferative inhibitors of Ki-67 and PCNA. ADMET properties, MD studies and toxicity prediction shows that current investigated ligands bind effectively with Ki-67 and PCNA without showing any toxicity. **Conclusions:** Current study concludes that eucalyptone with Ki-67 and sulfocostunolide B with PCNA made stable complexes and can be considered as novel inhibitors. In addition to that, these suggested ligands have also shown effective drug likeness and ADMET profile. Further, *in-vitro* and *in-vivo* studies are required to validate these findings.

INTRODUCTION

Cancer is a group of diseases consisting of a combination of genetic, epigenetic, signaling, and metabolic anomalies which critically disrupt the regular homeostasis of cell survival, growth and death [1]. Cancer is the second leading cause of death. The cancer diagnosis is difficult due to the wide range of symptoms that appear during different stages of cancer [2]. MRI scan, CT scan, ultrasound, biopsy, and X-rays are being used to detect abnormalities and presence of tumor within the body [3]. Besides these diagnostic tests, two other diagnostic biomarkers, Ki-67 (a marker of proliferation Kiel-67) and Proliferating Cell Nuclear Antigen (PCNA) are effective diagnostic tools as both these proteins are over-expressed in cancerous cells. Uncontrolled proliferation of cells is the one of the major hallmark of developing cancer, and expression of those genes that are involved in proliferation are up-regulated in cancerous cells [4]. Ki-67 and PCNA are regular biomarkers of proliferation that are usually used to measure the growth fraction of the population of a cell. Both proteins have proliferation markers characteristics as well as predictive and prognostic importance [5]. Molecular docking (MD) is structure-based in-silico method that is commonly used in drug discovery. In-silico docking enables to identify the novel bioactive compounds of high therapeutic interests and predicts interactions between ligand and receptor at the molecular level [6]. Currently, this computational technology is widely used for initial stages of drug design. For researchers, it is convenient to use the compound database to synthesize and complete pharmacological tests. It greatly reduces cost, time wastage and improves

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the efficacy of research in drug development [7]. For decades plants are a widespread natural product reservoir and have been used for the treatment of numerous ailments including cancer [8]. Sesquiterpene lactones (SLs) are the utmost dominant group among all the secondary metabolites that are present in plants. SLs displayed various biological activities such as anti-oxidant, anti-tumor, anti-microbial, and hepatoprotective activities that are reported in a various studies [9]. In current study, MD analysis between Ki-67, PCNA and five compounds of SLs has been carried out for evaluating their anticancer potential.

METHODS

Molecular docking was done by retrieval of ligands and proteins from databases, optimization of their conformations, binding of ligands with proteins and analysis of the interactions occurring between them [10, 11]. Crystal structure of Ki-67 (PDB ID: 5J28) and PCNA (PDB ID: 1VYM) were retrieved by using RSCB protein data bank and was prepared in PDBQT format by Autodock Vina. Five ligands namely sulfocostunolide A, sulfocostunolide B, eucalyptone, ilicol and ascleposide E were recovered in SDS-3D format by using PubChem Database and were also prepared PDBQT formats by AutoDock Vina. Afterwards, AutoDock vina 1.5.7 was used to dock these SLs with Ki-67 and PCNA. In this case, size of designed grid box was 40x40x40Å in X, Y, Z dimension, along with 0.375 spacing. With each ligand, both proteins generated nine diverse poses out of which only one pose is taken as probable binding mode due to its highest binding energy as given in the previous studies [12]. After analysis of MD, Biovia discovery studio visualizer was used for visualization of different interactions occurring between ligand and protein. Ligplot+ 4.5.3 was used for visualization of hydrophobic and hydrogen interactions. In addition to that, pharmacokinetic properties of ligands were analyzed by using pkCSM and SwissADME to assess their toxicity and drug likeness. For this purpose, SMILES of ligands were taken from PubChem and analyzed using pkCSM [13, 14]. pkCSM is a computational tool and used to predict ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of a candidate drug. These are the major pharmacokinetic properties for drug likeness of a molecule by giving canonical SMILES as an input. These properties can reduce the late stage failure or withdrawal of drug in drug discovery process to save money and time and ensuring the stability and safety of designed drug in future. Drug likeness scores by these physicochemical properties can be considered as first step of success for any drug candidate molecule [13].

RESULTS

Current study revealed that selected SLs strongly bind with proliferation marker proteins Ki-67 and PCNA. All the ligands showed good binding energy score as well as efficient binding interactions with respective proteins. Among all, eucalyptone with binding energy of -8.1 kcal/mol with Ki-67 while sulfocostunolide B with -6.4 kcal/mol binding energy with PCNA seemed to be the most potent proliferative proteins inhibitors (Table 1).

Table 1: Binding Affinities and Inhibition Constants of SLs with ki-67 and PCNA.

Ligands	Ki-67		PCNA	
	Binding Affinity	Inhibition Constant	Binding Affinity	Inhibition Constant
	Kcal/mol	µM	Kcal/mol	µM
Sulfocostunolide A	-7.4	3.57	-6.3	23.04
Sulfocostunolide B	-7.8	1.81	-6.4	19.4
Eucalyptone	-8.1	1.09	-6.1	32.3
Ilicol	-7.3	4.23	-5.6	75.4
Ascleposide E	-7.9	1.53	-6.1	32.3

Among all SLs, eucalyptone showed more hydrogen bonds with Ki-67. It binds with Ki-67 by forming seven hydrogen bonds with ARG221, ARG221, GLN249, ASP220, GLN249, ASP220 and ASP220 residues with bond distances of 2.66Å, 2.88Å, 2.17Å, 2.43Å, 2.61Å, 2.39Å and 2.75Å, respectively. Eucalyptone also formed an electrostatic bond with ASP220 (3.83Å) as shown in figure 1.

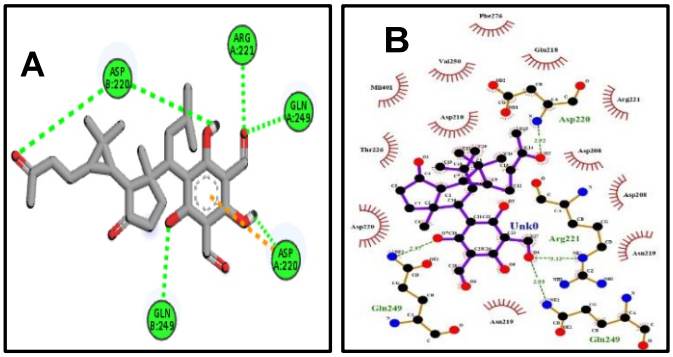

Figure 1: Two-dimensional view of docked eucalyptone with Ki-67 protein (a) visualization by discovery studio showed six hydrogen bonds and one hydrophobic interaction in eucalyptone-Ki67 complex. (b) Ligplot results verified the same interaction of eucalyptone with Ki-67.

Sulfocostunolide B strongly bounded by four hydrogen bonds with ARG149, ARG149, THR216 and ALA145 of PCNA via bond distances 2.51Å, 2.19Å, 2.48Å and 2.42Å respectively (Figure 2).

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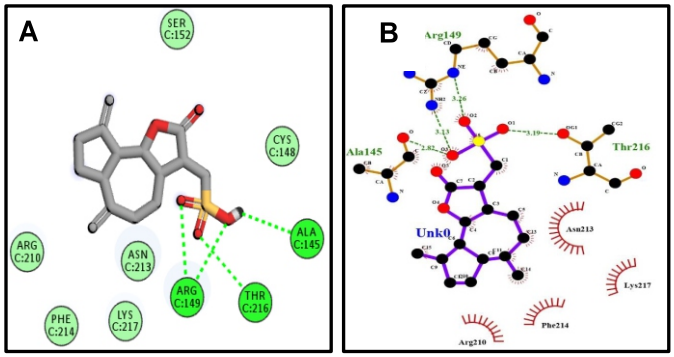

Figure 2: Two-dimensional view of docked sulfocostunolide-B with PCNA protein (a) visualization by discovery studio showed four hydrogen bonds between sulfocostunolide-B and PCNA complex (b) Ligplot results verified the same interaction of sulfocostunolide-B with PCNA.

For assessment of drug likeness of the selected ligands, Lipinski rule of 5 was employed as elaborated in table 2. This rule provides a guideline to predict the bioavailability of the drug candidate. If the drug candidate follows all the criteria of this rule then it is safe for oral administration and effective to use. For this purpose, it should have a molecular weight below 500 Dalton, a log P value not exceeding 5, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors and polar surface area should be less than 140 Å^2[15]. All our ligands have shown no violation than standard values as given in table 2.

Table 2: Lipinski Rule of Five Analysis of Selected Ligands

Ligands	Molecular Weight < 500 (g/mol)	H-Bond Acceptor < 10	H-Bond Donors < 5	log P < 5	Polar Surface Area (Å2)
Sulfocostunolide A	312.387	4	1	1.964	89.05
Sulfocostunolide B	312.387	4	1	1.964	89.05
Eucalyptone	486.605	7	3	5.184	128.97
Ilicol	238.371	2	2	2.892	40.46
Ascleposide E	388.457	8	4	-0.254	125.68

Properties of potential ligands were evaluated by ADMET analysis. ADMET analysis was carried out using pkCSM to ensure ADMET properties of potential drug candidates as given in Table 3. The ADMET profiling of eucalyptone and sulfocostunolide B was determined as they showed greater binding energy with Ki-67 and PCNA respectively. For absorption, water solubility of sulfocostunolide B and eucalyptone were -2.185 and -3.977 (log S) mol/L with 95.978 and 91.219 intestinal absorption respectively. Log value of volume distribution of sulfocostunolide B and eucalyptone were -0.503 and 0.068 (L/Kg) respectively. Substrate and inhibitors of CYP2D6 and CYP3A4 protein of both ligands were found to be absent expect CYP3A4 substrate of eucalyptone for metabolism. Total clearance of both candidate drugs were 0.009 and 0.24 Log/ml/min/kg for both drugs respectively with no OCT2 substrates. Both ligands showed no AMES and hepatotoxicity.

Table 3: Drug Likeness Prediction Using pk CSM Online Database Server for the Selected Ligands.

ADMET	Variables	Sulfocost-unolide B	Eucalyptone
Absorption	Water Solubility (LogS) ml/L	-2.185	-3.977
	Intestinal Absorption	95.978	91.219
	P-Glycoprotein I/II Inhibitors	No	Yes
Distribution	Log VDs (L/Kg)	-0.503	0.068
Metabolism	CYP2D6 Substrate	No	No
	CYP3A4 Substrate	No	Yes
	CYP2D6 Inhibitor	No	No
	CYP3A4 Inhibitor	No	No
Excretion	Total Clearance (Log ml/ min/ kg)	0.009	0.24
	Renal OCT2 Substrtae	No	No
Toxicity	AMES	No	No
	Max. Tolerable Dose (log mg/kg/day)	0.856	-0.203
	Hepatotoxicity	No	No

DISCUSSION

SLs display higher varieties in structure and exhibit many biological activities. SLs have been proved to exert anti-cancer efficiency and tumor cell cytotoxicity and are currently in clinical trials [16, 17]. In present study, docking results revealed that protein-ligand complexes have shown good binding affinities and hydrogen bonding. Current study revealed that selected ligands strongly bind with Ki-67 through different hydrogen, hydrophobic and electrostatic interactions, and inhibited Ki-67 efficiently in the same way as reported in previous studies as follows. In an *in-vitro* study, it has been shown that a natural compound arglabin reduces Ki-67 positive cells by inhibiting mTOR/Akt/PI3K pathway group. It increases SCC-4 cells growth, apoptosis and induces arrest. Arglabin induces apoptosis by chromosomal condensation, SCC-4 cell fragmentation, and bleb formation. These findings were further confirmed by in vivo studies and Ki-67 was down-regulated after treatment with arglabin indicating that the growth of OSCC cells was inhibited by arglabin which is SLs [18]. Recently reported in-vitro findings showed similar binding of other SLs such as costunolide Trilobolide-6-O-Isobutyrate (TBB) with Ki-67. Results revealed the inhibition of proliferation and HCC cell colony formation by TBB. Similarly, TBB inhibited the STAT3 signaling pathway which in turn influences and inhibited the expression and transcription of P21, Ki-67 and PCNA genes [19]. In another in-vivo study, Micheliolide (SLs) effected growth of tumor cells (AGS and N87 cells) of gastric cancer analyzed through an MTT assay. Results revealed that Ki-67 and PCNA expression in AGS and N87 was reduced significantly after treatment with Micheliolide [20]. These results are in accordance to our selected SLs as they inhibited the proliferation markers by MD analysis as well. Favorable bioavailability and drug-likeness of a drug is

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generally evaluated by Lipinski's rule of 5. All our selected ligands followed this rule as explained in methodology section. It confirms their bioavailability and oral administration. Eucalyptone showed deviation (logP=5.1849) from the threshold value (logP< 5.00). However, it is important to note that the Lipinski rule of 5 is a guideline rather than an absolute rule and deviations from these parameters can still result in successful drug candidates [21]. Absorbance of drug candidate was examined by analyzing various parameters such as water solubility (log S) mol/L, P-glycoprotein I/II inhibitor and intestinal absorption. Water solubility (log S) in mol/L measures drug's availability in aqueous solution. Higher value signifies higher absorbance and both drug candidates fall within its range of -4 to -2 mol/L [22]. P-glycoprotein I/II is an efflux membrane transporter which is responsible for hindering the absorption and bioavailability of chemotherapeutic drugs. P-glycoprotein I/II inhibitors have ability to enhance the consumption of potential drug many folds leading to adverse drug-drug interactions [23]. As shown in table 3, eucalyptone being an inhibitor compromise higher drug absorbance at the risk of unfavorable pharmacokinetic interactions. Both compounds exhibit intestinal absorption value greater than 30% indicating their significant absorption in intestine [24]. LogVDss (volume of distribution at steady state) ensures the steady concentration of drug in blood plasma and its ideal value must be in the range of -0.15 to 0.45. Both drug candidate's falls within this range and depict optimal values [25, 26]. Cytochrome P450 (CYP450) plays significant role in metabolism of drugs. Its two isoforms, CYP3A4 and CYP2D6, oxidize and modify chemical structures of drugs allowing their biotransformation. Sulfocostunolide B does not show any interaction with CYP450 isoforms. However, eucalyptone, being CYP3A4 substrate can facilitate elimination and clearance of drug from body yet it can also impose drug-drug interaction due to increased enzyme activity [26-28]. Both of the ligands are not renal OCT substrate which ensures reduced renal clearance leading to increased therapeutic effect. Total clearance represent sum of all clearance mechanism and both the ligands seemed to be eliminated from the body [29]. In addition to that, it is evident from table 3 that both the drug candidates are neither hepatotoxic nor AMES toxic. AMES toxicity assay analyze drug's ability to induce genetic mutations [30]. Both ligands possess fewer values for maximum tolerable dose. Lower values of maximum tolerable dose signifies maximum limit of drug's administration in the body so that it

CONCLUSIONS

In the current MD-aided study, we analyzed some SLs as potential inhibitors of cell proliferation markers of Ki-67 and PCNA. All these compounds showed effective binding energies and molecular interactions. However, eucalyptone and sulfocostunolide B can be considered to have more potential as a cancer cell proliferation inhibitors. In addition to that, both the suggested compounds have shown effective ADMET profile, drug likeness and bioavailability. To further validate their inhibitory effect, *in-vitro* and *in-vivo* investigations are required to have much deeper insights in their inhibition potential.

Authors Contribution

Conceptualization: MK
Methodology: IH, SG, EZ
Formal analysis: IH, AZ, EZ
Writing, review and editing: IH, MK, AZ, SG

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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