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In silico ADME and Toxicity Study of Some Selected Antineoplastic Drugs

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ABSTRACT

Cancer is a serious health problem that recognized as a group of diseases involving uncontrolled cell growth. Majority of cancer chemotherapeutic agents have serious toxicity profile. Due to this use of these agents are limited. Therefore, it is essential requirement for developing new chemotherapeutic agents to devoid toxicity. In this research work, we study the pharmacokinetic, toxicity and bioactivity profile of few selected chemotherapeutic agents by *In silico* method. These research investigations provide the lead for the development of new cancer chemotherapeutic agents with lesser toxicity and more effectiveness.

Keywords: TPSA (Topological Polar Surface Area), anticancer, *in silico* toxicity, GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, enzyme inhibitor.

INTRODUCTION

Cancer is a family of diseases involving uncontrolled cell growth with the potential to spread other body parts. Today, Cancer is a serious health problem of all over the world. There are various chemotherapeutic agents have been developed that are currently used for the management of cancer. [1] However, selectivity of the majority of chemotherapeutic agents is limited and they are one of the most toxic agents used in chemotherapy. [2] Majority of the chemotherapeutic agents have more profound effect on rapidly multiplying cells because the most important target of action is the nucleic acids and their precursors. Therefore, many tissues are affected by chemotherapeutic agents in dose-dependent manner.

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So, there is essential requirement for developing new cancer chemotherapeutic agents to devoid such toxic effects. The aim of this research work is to study pharmacokinetic, toxicity and bioactivity profile of some cancer chemotherapeutic agents by applying computational methods.

MATERIALS AND METHODS

In silico ADME study

There are various physicochemical descriptors and pharmacokinetic relevant properties of the cancer chemotherapeutic agents were evaluated by using the tool MolinspirationCheminformatics server (http://www.molinspiration.com). MolinspirationCheminformatics offers broad range of tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modeling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. This software also supports fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform.

Drug-likeness is described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs. These properties are mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features that influence the behaviour of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. The Lipinski rule of five deals four simple physicochemical parameter ranges (MWT ≤ 500, log P ≤ 5, H-bond donors ≤ 5, H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status. [3] These physicochemical features are associated with acceptable aqueous solubility and intestinal permeability.

***In silico* Toxicity study**

The toxicity of the adrenergic agents was evaluated by computational method using Pallas version 3.1 ADME-Tox prediction software pentium IV processor. This software tool was started by double click on the icon. The molecule to be predicted was drawn by double click on new option, and then molecule was subjected for evaluation of toxicity by selecting ToxAlert options. Various types of toxicities including oncogenicity, neurotoxicity, teratogenicity, immunotoxicity, etc. were generated and toxicity profile of molecule noted.

RESULTS AND DISCUSSION

There were eight cancer chemotherapeutic agents were selected and analyzed to drug-likeness (Lipinski's rule of five) which are given in Table 1.

All chemotherapeutic agents have molecular weight in the range (MWT ≤ 500) without doxorubicin. The compounds having low molecular weight are easily absorbed, diffused and transported as compared to high molecular weight compounds. With increase in molecular weight except certain limit, the bulkiness of the compounds is also increases comparably. [4] Methotrexate hasnumber of H-bond acceptors 13 and number of H-bond donors 7, so Methotrexate has two violations (H-bond donors ≤ 5, H-bond acceptors ≤ 10). Same as Doxorubicin has three violations and cisplatin has one violation. The MLogP (octanol / water partition co efficient) of all agents were calculated and were found to be within range according to Lipinski's rule. The MLogP value is used to calculate the lipophilic efficiency that measures the potency of drug. Therefore Octanol-water partition coefficient logP value is essential in rational drug design and QSAR studies. In the pharmacokinetic study, hydrophobicity of the compound is assessed by evaluating logP value because hydrophobicity plays a vital role in the distribution of the drug in the body after absorption. [5]

TPSA (Topological Polar Surface Area) is a very useful physiochemical parameter of compounds that gives the information about polarity of compounds. This parameter is evaluated for analyzing drug transport properties. Polar surface area is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen. [6] Percent absorption were also evaluated for all selected chemotherapeutic agents by %ABS = 109-(0.345 9 TPSA). [7] Molecular volume assesses the transport properties of the compound such as blood-brain barrier penetration. The number of rotatable bond was calculated and have found relevant. A compound which have more number of rotatable bond become more flexible and have good binding affinity with binding pocket.

Table 1: ADME Properties of Cancer Chemotherapeutic agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Methotrexate	$C_{20}H_{22}N_8O_5$	454.45	-1.97	210.55	13	7	9	387.36	36.36
Fluorouracil	$C_4H_3FN_2O_2$	130.08	-0.59	65.72	4	2	0	96.91	86.32
Cyclophosphamide	$C_7H_{15}Cl_2N_2O_2P$	261.09	0.76	41.57	4	1	5	209.00	94.65
Doxorubicin	$C_{27}H_{29}NO_{11}$	543.52	0.57	206.08	12	7	5	459.18	37.90
Cisplatin	$H_6Cl_2N_2Pt$	300.05	-4.58	55.28	2	6	0	103.04	89.92
Dacarbazine	$C_6H_{10}N_6O$	182.19	-0.13	99.74	7	3	3	160.16	74.58
Procarbazine	$C_{12}H_{19}N_3O$	221.30	1.12	53.15	4	3	5	223.55	90.66
Oxaliplatin	$C_8H_{14}N_2O_4Pt$	114.19	-0.55	52.05	2	4	0	125.23	91.04

Table 2: Bioactivity of Cancer Chemotherapeutic agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor Ligand	Protease inhibitor	Enzyme inhibitor
Methotrexate	0.51	0.23	0.38	-0.38	0.27	0.72
Fluorouracil	-2.60	-1.95	-2.61	-3.04	-3.15	-1.56
Cyclophosphamide	-0.65	-0.38	-0.59	-0.95	-0.33	0.53
Doxorubicin	0.20	-0.20	-0.07	0.32	0.67	0.66
Cisplatin	-4.15	-3.96	-4.12	-4.35	-4.13	-4.01
Dacarbazine	-0.56	-0.39	-0.18	-2.44	-0.96	0.06
Procarbazine	-0.19	-0.07	-0.46	-0.77	-0.11	-0.01
Oxaliplatin	-2.58	-2.41	-2.70	-3.41	-2.33	-2.25

Table 3: Toxicity Profile of Cancer Chemotherapeutic agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Methotrexate	Highly Probable	76	76	53	19	0	29	0	0
Fluorouracil	Highly Probable	76	76	0	34	0	0	0	0
Cyclophosphamide	Highly Probable	79	76	79	0	0	0	0	0
Doxorubicin	Highly Probable	91	77	91	19	53	0	0	29
Cisplatin	Not Probable	0	0	0	0	0	0	0	0
Dacarbazine	Highly Probable	76	76	0	17	0	0	0	0
Procarbazine	Highly Probable	76	76	67	29	47	0	0	0
Oxaliplatin	Highly Probable	76	76	0	0	0	0	0	0

Bioactivity of all selected chemotherapeutic agents was evaluated against six different protein structures. Biological activity is predicted by bioactivity score that are categorized under three different ranges-

a) If bioactivity score is more than 0.00, having considerable biological activity.
b) If bioactivity score is 0.5 to 0.00, having moderately activity.
c) If bioactivity score is less than -0.50, having inactivity. [8]

The result of this investigation was found that the chemotherapeutic agents are biologically active and have physiological effect. The bioactivity score profile of the all selected agents is given in Table 2. Cisplatin, doxorubicin, fluorouracil, oxaliplatin and procarbazine having bioactivity score against GPCR ligand which indicates they could bind more effectively with GPCR. The bioactivity score provide the information about the binding cascade of the drugs that is used for the development of a new functional drug with increased binding selectivity profile and less undesirable effects.

All selected chemotherapeutic agents were evaluated to toxicity profile and given in Table 3. Majority of the agents were found to be highly probable to toxicity. Only cisplatin was found to be not probable to toxicity.

These research findings provide the lead for the design and development of new cancer chemotherapeutic agents. Currently, all existing chemotherapeutic agents having serious toxicity profile. Therefore, it is essential that the development of new cancer chemotherapeutic molecules with lesser side effects and toxicity. Computational analysis of all selected chemotherapeutic agents gives the information about the pharmacokinetics of the existing drugs that provide the lead for development of functional drug with more effectiveness and lesser toxicity.

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