Predicting ADMET Properties for Commercially Available Anticancer Drugs

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Abstract: Drug discovery and development is a tedious process which involves high man power, costly chemicals and resources. Failure of drugs at late stage clinical trials is the common problem that occurs at current scenario. Though tremendous input has been given to discover new drugs, overcoming the drug failures and occurrence of adverse side effects need to be rectified. Predicting Absorption, Distribution, Metabolism and Excretion (ADME) properties at early stage with in silico tools would be much promising.In this paper, commercially available anticancer drugs were taken and their ADME properties were predicted with SWISS ADME. The results shows that most of the drugs possess lower solubility, low GL absorption and lower penetration to blood brain barrier. The obtained results could be a model to develop new drugs and to design anticancer drugs that eventually prevent late stage clinical trials.

Keywords: ADME, anticancer, drugs, SWISS ADME, clinical trials

I. INTRODUCTION

Drug discovery involves tremendous resources, chemicals and man power. The clinical science has contributed high progress in medicine for last five decades. However, various side effects were observed with drugs that are at the last stages of clinical trials. A success of the drug not only relies on the development of a drug molecule for its target, but also on its safety and efficacy with least side effects for prolonged time. Though numerous researches are focusing to develop anti-cancer drugs [1], the drugs with least side effect after commercialization are very few till date. Anticancer drugs are targeted towards their target site in number of ways such as by conjugating the biomolecules [2, 3] with nanoparticles [4], using nanoparticles for optimal delivery, utilizing nanobhasmas [5], nanonutraceuticals [6–8], The major reason behind is the failure to predict ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties at the early stages of drug development. Further, ADMET prediction with in vitro and in vivo methods are time consuming, which is the reason for lack of data on ADMER properties of a drug [9] .

Computational ADMET prediction which involves both in vivo and in vitro methods renders easy and rapid ADMET prediction and eventually helps to reduce the side effect issues. As there is a need to reduce the working models with animals, such as in REACH project, computational ADMET prediction will be of a promising advantage. In silico ADMET prediction such as quantitative structure–activity relationships (QSARs/QSPRs) are being in use to predict ADMET properties. Advances in technology paves way out with numerous online servers and standalone software available to predict ADMET [10]. Certain physic-chemical properties [11] such as drug likeliness or lead likeliness, solubility, Lipinski rule of five [12] are available as free in most of the online and commercial packages. Apart from physic-chemical properties, being substrate to metabolizing enzymes such as CYP 450s [13], plasma binding proteins, toxicity towards the environment are also highly considered [14].In the present work, the ADMET properties of commercially available anticancer drugs were predicted to identify their properties that are the causes for side effects.

II. MATERIALS AND METHODS

Collection of anticancer drugs

The list of commercially available anticancer drugs were retrieved from the National cancer institute (NIH) [15]. NIH consists of more than 500 anticancer drugs. The obtained list were consolidated based on the cancer type in an excel file for further use.

Ligand preparation

The structure of drugs were fed in computational tools in mol file format. Hence to obtain the mol. file format, the canonical smiles of each drug was retrieved from the pubchem database manually. Pubchem database consists of information about the molecular structure, chemical names, molecular formula, molecular weight, drug information, clinical trials, 2d conformer and 3d structure of the drugs [16]. The canonical smiles available for each drug was collected and documented with their respective cancer drugs. The smiles are converted to mol. file format with CORINA server [17].

ADMET prediction

The ADMET properties of each anticancer drug was predicted with SWISS ADME [18]. Input data was given as mol. files and each ADMET property was determined.

Results and discussion

NIH consists of more than 500 anticancer drugs which are segregated based on the cancer type and alphabetical order [19]. The names of the drug for each cancer type was obtained and their respective canonical smiles were

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downloaded. The smiles were converted to mol files with CORINA server and were submitted in SWISS ADMET.

The result contains the name of the molecule with important ADME parameters such as molecular weight, solubility, Blood Brain Barrier (BBB), bioavailability, synthetic accessibility, etc., were obtained for each anticancer drug. Based on the results retrieved from the Egan boiled egg model [20] which is graphical representation of the predicted properties, maximum drugs that exceed the ADMET cut of limits were alone represented here.

Drugs beyond ADMET cut off limits

Anticancer drugs of Acute Lymphoblastic Leukemia (ALL) were shown in table 1. Drugs that are out of range ie., exhibiting ADME properties beyond the permissible limits appears outside the white egg of the boiled egg model (Figure 1). The list of drugs with their ADME properties were shown in table 1.

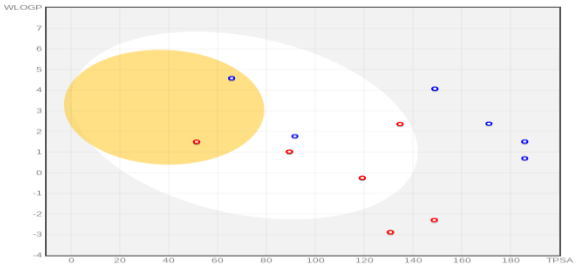

Fig 1: Boiled egg model - Acute lymphoblastic leukemia

Table 1: ADME properties of Acute lymphoblastic leukemia anticancer drugs

Acute lymphoblastic leukemia	MW	TPSA	M LogP	Solubility	GI	BBM	CYP inhibitors	Bioavailability	Synthetic accessibility
Methotrexate	454.44	210.54	-1.153	soluble	Low	No	No	0.11	3.58
Clofarabine	303.68	119.31	-0.84	soluble	High	No	No	0.55	3.93
cytarabine	243.22	130.83	-2.29	Very soluble	Low	No	No	0.55	3.84
Ozogamicin	1681.68	486.4	-2.57	Poorly soluble	Low	No	No	0.17	10
Mesylate	589.71	149.03	1.52	Soluble	Low	No	No	0.17	4.19
Mercaptopurine	152.18	89.45	-1.16	Very soluble	High	No	No	0.55	1.72
Dasatinib	488.01	134.75	1.75	Moderately soluble	High	No	Yes	0.55	3.83

ADME of breast cancer drugs shows 24 molecules to be beyond the ADME values. Drugs such as Methotrexate, Everolimus, Epirubucin hydrochloride, Mesylate, Fluvestrant, Eribulinmesylatre exhibits higher values of ADME. All these drugs has lower GI absorption rate, lower penetration to BBB and lower bioavailability.

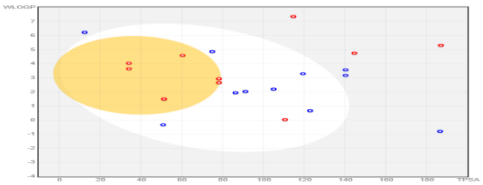

Fig 2: Boiled egg model for Breast cancer

Table 2: ADME of breast cancer drugs

Breast cancer	MW	TPSA	M LogP	Solubility	GI	BBM	CYP Inhibitors	bioavailability	Synthetic accessibility
Methotrexate	454.44	210.54	-1.13	Soluble	low	No	No	0.11	3.58
Everolimus	958.22	204.66	0.57	soluble	low	No	No	0.17	10
Epirubucin HCL	579.98	206.77	-1.9	Poorly soluble	low	No	No	0.17	5.88
Mesylate	826	209.15	-0.63	Moderately soluble	Low	No	No	0.17	10
Fluvestrant	606.77	76.74	5.93	soluble	Low	No	No	0.17	5.58
Eribulin mesylatre	826	209.95	-0.63	Low soluble	Low	No	No	0.17	10
LPF	454.44	210.54	-1.13	soluble	Low	No	No	0.11	3.58
Pacitaxel	853.91	221.19	1.7	soluble	Low	No	No	0.17	8.34
Docetaxel	807.88	224.45	1.06	Poorly soluble	Low	No	No	0.17	8.39
Vinblastine sulfate	909.05	237.08	1.3	Moderately so	Low	No	No	0.17	9.98
Capecitabine	359.35	122.91	0.53	soluble	High	No	No	0.55	4.67

Likewise, the drugs that are commercially available for lung cancer also exhibits various ADME properties.Twenty five drugs were shown to occur outside the yellow part of boiled egg model (Figure) indicating that they are the out of range molecules. Most of the drugs are poorly soluble, as shown in table which usually results in lower penetration of drug inside the body and hence higher intake of drug. This maximum dosage of anticancer drug will usually results in nausea, ulcer and other side effects.

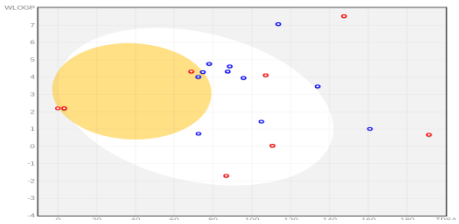

Fig 3: Boiled egg model-Lung cancer

Table 3: ADME of Lung cancer drugs

Lung cancer	MW	TPSA	M Log P	Solubility	GI	BBM	CYP inhibitors	Bioavailability	Synthetic accessibility
Methotrexate	454.44	210.54	-1.13	soluble	Low	No	No	0.11	3.58
Everolimus	958.22	204.66	0.57	Poorly soluble	Low	No	No	0.17	10
PFS	454.44	210.54	-1.13	soluble	Low	No	No	0.11	3.58
Paclitaxel	853.91	221.19	1.7	Poorly soluble	Low	No	No	0.17	8.34
Docetaxel	807.88	224.45	1.06	Moderately soluble	Low	No	No	0.17	8.39
Etoposide phosphate	668.54	217.17	-0.81	Soluble	Low	No	No	0.11	6.69
Crizotinib	450.34	77.99	3.22	Poorly soluble	High	No	Yes	0.55	3.77

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Most of the drugs of Hodgkin Lymphoma and Non-Hodgkin Lymphoma exhibited ADME properties beyond the permissible limits. The drugs were found to be soluble, however they lacked GI absorption with lower bioavailability and synthetic accessibility. The molecular weight (MW) of few drugs were found to be much higher than the MW stated in Lipinski rule of five. Drugs such as Bleomycin, Vinblastine sulfate and Tiuxetan had MW of 1415 Da, 909.05 Da and 569.56 Da respectively.

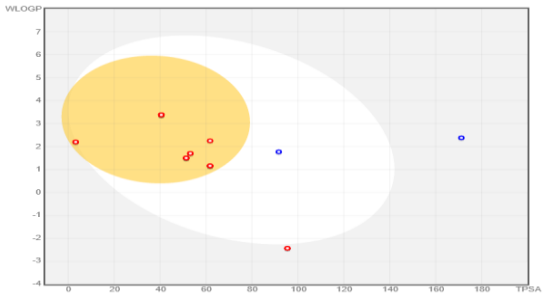

Fig 4 Boiled egg model – Hodgkin lymphoma

Table 4: ADME of Hodgkin lymphoma anticancer drugs

Hodgkin lymphoma	MW	TPSA	MlogP	Solubility	GI	BBM	CYP Inhibitors	bioavailability	Synthetic accessability
Bleomycin	1415.55	708.85	-10.28	Soluble	Low	No	No	0.17	10
Dacarbazine	182.18	95.44	-0.74	Soluble	Low	No	No	0.55	3.38
Procarbazine HCL	257.76	53.10	2.07	Moderately soluble	High	Yes	No	0.55	1.65
Vinblastine sulfate	909.05	237.08	1.3	Soluble	Low	No	No	0.17	9.98

III. CONCLUSION

Our results conclude that most of the commercially available anticancer drugs possess lower solubility, bioavailability, lower penetration to blood brain barrier, GL absorption and higher synthetic accessibility. Hence, these results can be used as a model to develop new drug candidates that possess unique ADME properties with respective cut off limits for each ADME parameter.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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