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The natural anti-tubercular agents: *In silico* study of physicochemical, pharmacokinetic and toxicological properties

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ABSTRACT

The purpose of the present study is to explore the physicochemical, pharmacokinetic and toxicological properties and to correlate the calculated physicochemical properties with the absorption and distribution profile of seven natural anti-tubercular agents such as 6a,7-dehydro-N-formylnornantenine (DNF), Aristololactam (AL), Isoambreinolide (IA), Andrographolide (AGD), 8,8'-Biplumbagin (BPG), Plumericin (PC) and Tiliacorine (TC). The physicochemical properties such as intrinsic solubility (solubility of unionized form) in water (logS), partition coefficient (logP), H bond donor and acceptor count were calculated using MarvinSketch software. The pharmacokinetic and toxicological properties were calculated using online server PreADMET. The calculated aqueous solubility demonstrated that all the seven compounds possess limited solubility which ranged from very slightly soluble to practically insoluble. The calculation of partition coefficient suggested that all the compounds are lipophilic in nature and have higher affinity to reside in *n*-octanol than in water. The human intestinal absorption (HIA), Caco-2 cell penetrability, plasma protein binding (PPB) and C_{brain}/C_{blood} of the seven compounds were ranged from 94.89% - 100.00%, 20.18 - 54.75 nm/s, 73.52% - 100.00% and 0.353 - 2.331, respectively. The computed metabolism demonstrated that DNF, AL, IA, PC and TC are substrate for cytochrome P450 3A4. However, all the compounds displayed inhibitory characteristics against cytochrome P450 3A4. The virtual screening also demonstrated that AL, PG and BPG are 2C19 inhibitors and all the natural agents except DNF are 2C9 inhibitors. In phase II reaction, IA, PG and DNF, AL, PG, BPG are the substrates for UDP-glucuronosyltransferase (UGT) and sulfotransferase (SULT), respectively. In the *in silico* mutagenicity and carcinogenicity investigations, all the compounds except TC exhibited mutagenicity. Among all the natural anti-tubercular agents only DNF and TC demonstrated carcinogenicity in both mouse and rat models. The AL and PG were carcinogenic only in mouse but in rat model they were noncarcinogenic. On the other hand, IA, BPG and PC were noncarcinogenic in both mouse and rat model. In addition, the risk of inhibition of human ether-a-go-go-related (hERG) gene was varied from low to medium risk. Our computed properties may be assistance for the development of promising candidates to combat *M. tuberculosis* with better pharmacokinetic and toxicological profile.

INTRODUCTION

Mycobacterium tuberculosis is a pathogenic bacterium that causes infectious disease called tuberculosis. This disease is spreading all over the world. Each year 8.8 million and 1.6 million new infections and deaths, respectively are taken place due to *M. tuberculosis* (Luckner *et al*., 2010). The emergence of resistant strain of *M. tuberculosis* against isoniazid and rifampicin is contributing to the spread and worsening the situation by extending the therapy from 6 months to nearly 2 years and thereby increasing

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the cost for therapy to about 20 times (Luckner *et al*., 2010). Multidrug resistant strains of *M. tuberculosis* demands new drugs to restrain the spreading control of tuberculosis. The natural system always serve as a repository and generally mankind always looks into actinomycetes (Mahajan *et al*., 2011; Adegboye and Babalola, 2013; Patel *et al*., 2014), fungi (Smith and Ryan 2009; Aly *et al*., 2011), cyanobactria (Singh *et al*., 2011) and plants (Abdallah, 2011; Katiyar *et al*., 2012) for the new drug candidates. Numerous drugs and chemical agents have already been identified and the identification process is still on ongoing.

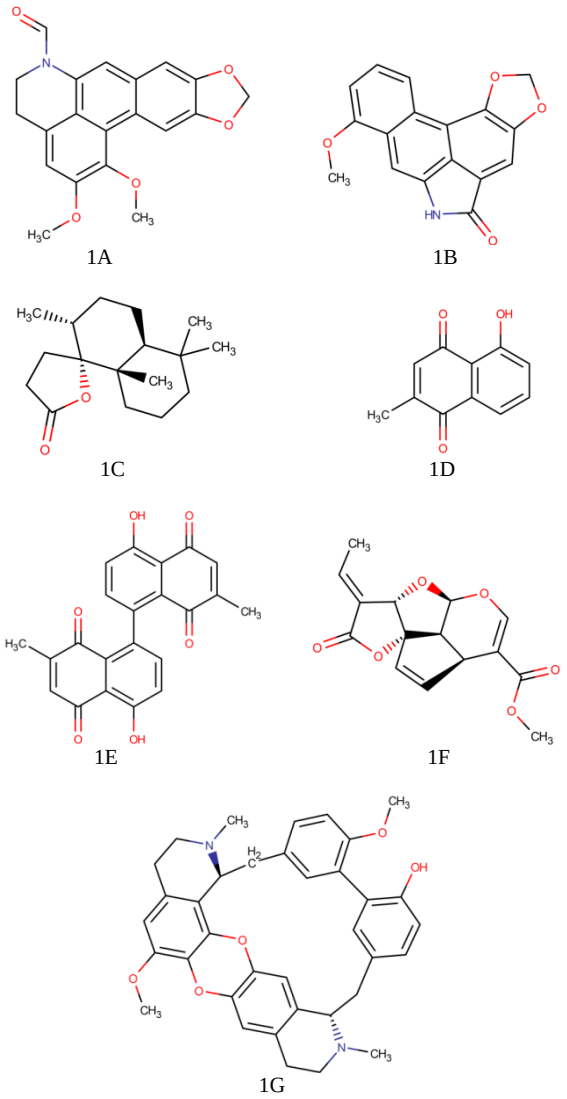

Fig. 1: Structure of (1a) 6a,7-Dehydro-N-formylnornantenine (DNF), (1b) Aristololactam (AL), (1c) Isoambreinolide (IA), (1d) Andrographolide (AGD), (1e) 8,8'-Biplumbagin (BPG), (1f) Plumericin (PC) and (1g) Tiliacorine (TC).

The long-term use of synthetic anti-tubercular agents displayed adverse drug reactions on patients which lead to interest in herbal medications. Herbal medicines are naturally occurring chemical agents which can be used in the form of whole plant or its particular part. The fewer adverse reactions, activity against several diseases and low cost are the major advantages of herbal medications. Several herbal plants and their isolated compounds are reported to be active against *M. tuberculosis* (Pandit *et al*., 2015). The 6a,7-Dehydro-N-formylnornantenine (DNF), Aristololactam (AL), Isoambreinolide (IA), Andrographolide (AGD), 8,8'-Biplumbagin (BPG), Plumericin (PC) and Tiliacorine (TC) are the natural compounds reported to be effective against tuberculosis (TB) (Serkan *et al*., 2012; Sureram *et al*., 2012; Tiwari *et al*., 2013; Kumar *et al*., 2013; Uc-Cachon *et al*., 2014; Prabu *et al*., 2015). However, literature survey revealed that no report on the physicochemical, pharmacokinetic and toxicological properties of these compounds has been reported. In this study, we computationally investigated (a) physicochemical properties such as intrinsic solubility (solubility of unionized form) in water (logS), partition coefficient (logP), H bond donor and acceptor count, (b) pharmacokinetic properties like human intestinal absorption (HIA), cellular permeability using Caco-2 cell model, skin permeability (P_{Skin}), plasma protein binding (PPB), penetration of the blood brain barrier (BBB) and (c) toxicological properties including mutagenicity, carcinogenicity and risk of inhibition of human ether-a-go-go-related (hERG) gene. The purpose of this study was to explore the physicochemical, pharmacokinetic and toxicological properties and to correlate the calculated physicochemical properties with the absorption and distribution profile of DNF, AL, IA, AGD, BPG, PC and TC (Figure 1). These computed properties may be of assistance for the development of promising candidates to combat *M. tuberculosis* with better pharmacokinetic and toxicological profile.

METHODOLOGY

Physicochemical properties

The intrinsic solubility (solubility of unionized form) in water (logS), partition coefficient (logP), H bond donor and acceptor count of 6a,7-Dehydro-N-formylnornantenine (DNF), Aristololactam (AL), Isoambreinolide (IA), Andrographolide (AGD), 8,8'-Biplumbagin (BPG), Plumericin (PC) and Tiliacorine (TC) were calculated using MarvinSketch 15.06.29 (ChemAxon (http://www.chemaxon.com)). The calculation of partition coefficient was conducted by applying both consensus and ChemAxon methods as implemented in MarvinSketch 15.06.29.

Pharmacokinetic and toxicological properties

The pharmacokinetic and toxicological properties were calculated using online server PreADMET (https://preadmet.bmdrc.kr/). This server enables to calculate pharmacokinetic and toxicological properties of chemical agents (Cunha *et al*., 2015). The pharmacokinetic properties such as human intestinal absorption (HIA), *in vitro* cellular penetrability using Caco-2 cell model, skin permeability (P_{Skin}), plasma protein binding (PPB) and penetration of the blood-brain barrier (BBB), interaction with P-glycoprotein (Pgp) and metabolism (both phase I and phase II) were calculated and predicted. However, virtual screenings were also performed to evaluate toxicological properties including mutagenicity, carcinogenicity and risk of inhibition of human ether-a-go-go-related (hERG) gene.

Table 1: physicochemical property of natural anti-tubercular agents.

Compound Name	Molecular formula	Molecular weight	Intrinsic aqueous solubility		Partition coefficient (logP)		H bond donor	H bond acceptor
			logS	mg/mL	Consensus	ChemAxon		
6a,7-Dehydro-N-formylnornantenine (DNF)	$C_{20}H_{17}NO_5$	351.1	-5.89	0.0005	2.35	2.21	0	5
Aristololactam (AL)	$C_{17}H_{11}NO_4$	293.1	-6.01	0.0003	2.54	2.49	1	4
Isoambreinolide (IA)	$C_{17}H_{28}O_2$	264.2	-4.5	0.0084	4.28	4.02	0	1
Plumbagin (PG)	$C_{11}H_8O_3$	188.0	-2.83	0.2781	2.24	1.69	1	3
8,8'-Biplumbagin (BPG)	$C_{22}H_{14}O_6$	374.1	-6.55	0.0001	4.15	3.01	2	6
Plumericin (PC)	$C_{15}H_{14}O_6$	290.1	-3.25	0.1631	1.53	1.85	0	4
Tiliacorine (TC)	$C_{36}H_{36}N_2O_5$	576.3	-6.29	0.0003	6.16	5.64	1	5

RESULTS AND DISCUSSION

Physicochemical properties

The intrinsic aqueous solubility (logS), partition coefficient (logP), H bond donor and acceptor count of the investigated natural anti-tubercular agents are presented in Table 1. The table suggests that all the compounds possess limited aqueous solubility which ranged from very slightly soluble to practically insoluble (Sinko, 2010). This result is also supported by the calculation of partition coefficient which indicates that all the tested compounds are lipophilic in nature and have higher affinity to reside in *n*-octanol than in water i.e. all the compounds will pass the plasma membrane easily.

Pharmacokinetic study

The pharmacokinetic studies such as absorption, distribution and metabolism of DNF, AL, IA, AGD, BPG, PC and TC were performed using online server PreADMET (https://preadmet.bmdrc.kr/). The calculated absorption, distribution and metabolism parameters are presented in Table 2, Table 3 and Table 4, respectively.

The calculated human intestinal absorption (HIA) (Table 2) was ranged from 94.89% to 100.00% which suggest that all the tested compounds are well absorbed through the intestinal cell (Yee, 1997).

Table 2: Absorption characteristics of natural anti-tubercular agents.

Compound Name	Absorption characteristics		
	HIA (%)	P_{Caco-2} (nm/s)	P_{skin}
6a,7-Dehydro-N-formylnornantenine (DNF)	97.37	42.46	-4.41
Aristololactam (AL)	96.55	21.12	-4.37
Isoambreinolide (IA)	100.00	53.66	-1.58
Plumbagin (PG)	95.25	20.18	-3.06
8,8'-Biplumbagin (BPG)	94.89	20.58	-3.27
Plumericin (PC)	96.05	23.15	-4.29
Tiliacorine (TC)	97.49	54.75	-3.57

In addition, all the compounds exhibited high permeability (Yazdanian *et al*., 1998) as absorption values through Caco-2 cell (P_{Caco-2}) was within 20.18 - 54.75 nm/s. The skin permeability (P_{Skin}) is a vital parameter for the assessment of drugs and chemical that might require transdermal administration. All the compounds were found to be impermeable through skin since the calculated P_{Skin} value was negative.

The distribution properties were assessed by evaluating the brain to blood partition coefficient (C_{brain}/C_{blood}), plasma protein binding (PPB) and interaction with the P-glycoprotein (Pgp). The calculated values of PPB were 73.52% to 100.00% (Table 3). Generally compounds with more than 90% of PPB are classified as strongly bound chemicals whereas less than 90% are weakly bound chemicals (https://preadmet.bmdrc.kr/adme-prediction/). Therefore, among all the agents IA, PG and BPG bound strongly with plasma protein whereas DNF, AL, PC and TC are weakly bound chemicals. The C_{brain}/C_{blood} values were 0.353 to 2.331. Based on C_{brain}/C_{blood} ratio all chemicals fall under three categories namely high absorption to CNS (C_{brain}/C_{blood} value more than 2.0), middle absorption to CNS (C_{brain}/C_{blood} value within 2.0 - 0.1) and low absorption to CNS (C_{brain}/C_{blood} value less than 0.1) (Xiao-lei *et al*., 2005). The ratio of C_{brain}/C_{blood} suggests middle to high absorption of these agents to CNS indicating moderate to higher ability to cross blood brain barrier (BBB).

Table 3: Distribution characteristics of natural anti-tubercular agents.

Compound Name	Distribution characteristics			
	PPB (%)	C_{brain}/C_{blood}	P-Glycoprotein (Inhibition)	P-Glycoprotein (Substrate)
6a,7-Dehydro-N-formylnornantenine (DNF)	73.52	1.277	Non	No
Aristololactam (AL)	80.24	1.368	Non	No
Isoambreinolide (IA)	97.49	2.331	Inhibitor	No
Plumbagin (PG)	100.00	0.851	Non	No
8,8'-Biplumbagin (BPG)	98.35	1.036	Inhibitor	Substrate
Plumericin (PC)	76.21	0.353	Non	No
Tiliacorine (TC)	79.91	0.789	Inhibitor	Substrate

P-glycoprotein (Pgp), produced from the multi drug resistance (MDR) gene and an ATP dependent efflux transporter that affects the absorption, distribution and excretion of clinically important drugs (Schinkel, 1999). The Pgp over-expression may lead MDR which is the main cause of failure of cancer chemotherapy and reduced efficacy of antibiotics (Kim *et al*., 1998; Cabrera *et al*., 2006).

The prediction of Pgp substrates aids early detection and elimination of chemical agents of low effectiveness or high potential of MDR (Wang *et al*., 2005; de Cerqueira *et al*., 2006). Identification of drugs that are Pgp substrates is essential for drug discovery, but it is primarily done through laborious *in vitro* and *in vivo* investigations (Joung *et al*., 2012).

Table 4: Metabolic (Phase I and Phase II) characteristics of natural anti-tubercular agents.

Compound Name	Metabolism							
	Phase I						Phase II	
	Cytochrome P450 2C19 (Inhibition)	*Cytochrome P450 2C9 (Inhibition)*	*Cytochrome P450 2D6 (Inhibition)*	*Cytochrome P450 2D6 (substrate)*	*Cytochrome P450 3A4 (Inhibition)*	*Cytochrome P450 3A4 (substrate)*	UDP-glucuronosyltransferase (UGT)	Sulfotransferase (SULT)
6a,7-Dehydro-N-formylnornantenine (DNF)	Non	Non	Non	Non	Inhibitor	Substrate	Non-substrate	Substrate
Aristololactam (AL)	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Non-substrate	Substrate
Isoambreinolide (IA)	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Substrate	Non-substrate
Plumbagin (PG)	Inhibitor	Inhibitor	Non	Non	Inhibitor	Non	Substrate	Substrate
8,8'-Biplumbagin (BPG)	Inhibitor	Inhibitor	Non	Non	Inhibitor	Non	Non-substrate	Substrate
Plumericin (PC)	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Substrate	Non-substrate
Tiliacorine (TC)	Non	Inhibitor	Non	Substrate	Inhibitor	Substrate	Non-substrate	Non-substrate

Table 5: Toxicological properties of natural anti-tubercular agents.

Compound Name	Mutagenicity (Ames test)	Carcinogenicity		hERG inhibition
		Mouse	Rat	
6a,7-Dehydro-N-formylnornantenine (DNF)	Mutagen	Negative	Negative	Medium risk
Aristololactam (AL)	Mutagen	Negative	Positive	Medium risk
Isoambreinolide (IA)	Mutagen	Positive	Positive	Low risk
Plumbagin (PG)	Mutagen	Negative	Positive	Low risk
8,8'-Biplumbagin (BPG)	Mutagen	Positive	Positive	Medium risk
Plumericin (PC)	Mutagen	Positive	Positive	Low risk
Tiliacorine (TC)	Non-Mutagen	Negative	Negative	Medium risk

Computational classification model can be used to screen molecules and predict the likeliness to be substrate for Pgp (Joung *et al*., 2012). The *in silico* screening revealed that BPG and TC is a dual inhibitors and substrates for Pgp. on the other hand, IA will act as an inhibitor of Pgp. This proves that IA is likely to be active in cells expressing high levels of Pgp.

The computed metabolism (Table 4) demonstrated that DNF, AL, IA, PC and TC are substrate for cytochrome P450 3A4. However, all the compounds displayed inhibitor characteristics against cytochrome P450 3A4. This is because due to complex modulatory interactions with the cytochrome P450 3A4 which make them to function as combinations of substrate and inhibitor (Zhou, 2008). The virtual screening also demonstrated that AL, PG and BPG are 2C19 and all the natural agents except DNF are 2C9 inhibitors. In phase II reaction, the substrates for UDP-glucuronosyltransferase (UGT) are IA and PG and the substrates for sulfotransferase (SULT) are DNF, AL, PG and BPG.

Toxicological study

Table 5 shows the results of mutagenic (Ames test) and carcinogenic (using mouse and rat model) properties of DNF, AL, IA, AGD, BPG, PC and TC. Toxicological investigation of drug candidates is one of the key steps for drug discovery. This means that the toxicity study is very important for new compounds.

The Ames test is widely used and accepted test to evaluate the mutagenicity of a chemical agent. In this test, different strains of *Salmonella typhimurium* bacterium with mutations in genes involved in histidine synthesis were used and the test compound is considered to be mutagenic if it enables the mutated bacterium to grow histidine-exempt medium i.e. if it stimulates the reversion process (Mortelmans and Zeiger, 2000). In this *in silico* mutagenicity investigations all the compounds except TC exhibited positive prediction i.e. mutagenic compound.

In carcinogenicity study, the PreADMET server was utilized to predict the carcinogenicity of chemical agent. The data generated from the *in vivo* carcinogenicity tests for mice and rats for 2 years of the National Toxicology Program (NTP) and the USA/FDA are used to build this server.

In the prediction of carcinogenicity negative prediction indicates there is evidence of carcinogenic activity whereas positive means the tested compound does not exhibit carcinogenic activity. Among all the natural anti-tubercular agents only DNF and TC demonstrated carcinogenicity in both mouse and rat model. The AL and PG were carcinogenic only in mouse but in rat model they showed positive prediction. On the other hand, IA, BPG and PC were non carcinogenic in both mouse and rat model. The risk of inhibition of human ether-a-go-go-related (hERG) gene was varied from low to medium. Inhibition of the hERG gene has been linked to long QT syndrome (Sanguinetti *et al*., 2006). The results have been in summarized in Table 5.

CONCLUSION

The calculated physicochemical properties demonstrates that all the screened compounds are lipophilic in nature and obeyed Lipinski's rule of 5 (Lipinski *et al*., 2001) except

tiliacorine (TC) which has partition coefficient value above 5 (logP). This lipophilicity explains why these compounds possess high human intestinal absorption (HIA), Caco-2 cell permeability and ability to cross BBB i.e. likeliness to be CNS active. Further, among all the compounds the BPG and TC demonstrated dual activity against P-glycoprotein i.e. both can act as inhibitor and substrate of P-glycoprotein similar to Quinidine (Zhou, 2008). On the other hand, virtual screening suggests that IA is a Pgp inhibitor and hence, co-administration of IA with drugs which are Pgp substrate would be therapeutically advantageous (Zhou, 2008). The prediction of metabolic characteristic displayed that DNF, AL, IA, PC and TC are substrates for cytochrome P450 3A4 and in phase II reaction, IA, PG and DNF, AL, PG, BPG are the substrates for UGT and SULT, respectively. The toxicological investigation showed that all the compounds except TC are mutagenic. However, a mutagenic compound may not be a carcinogen which is supported by the carcinogenicity investigation where IA, BPG and PC were non carcinogenic in both mouse and rat models.

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