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Physicochemical Study of Secondary Metabolites of Medicinally Important Fungi

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A B S T R A C T

Enormous metabolic versatility and richness of secondary metabolism is one of the most characteristic traits of fungi. These secondary metabolites are importantly required during various physiological processes, such as to combat the immune system, to acquire essential micronutrients, to compete in the environment and hosts, and pathogenicity. The fungal secondary metabolites are of diverse nature in chemical structures and biological activities. The functional efficiency of these secondary metabolites depends on physicochemical properties of the molecules. The physicochemical properties of fungal secondary metabolites were calculated and analysed to study its relation with functions and biological role. The analyses suggest varied pattern of correlation between molar refractivity, topological polar surface area and water solubility of secondary metabolites. Based on overall result it has inferred that the above characteristic physicochemical parameters may provide the chemical characteristics and functional specificity of a secondary metabolite.

Introduction

Fungi produce several small organic, bioactive natural products called secondary metabolites (Keller *et al.*, 2005; Bills *et al.*, 2017). The production of secondary metabolites is not necessary for the normal growth of fungi; however, it aid survival in harsh environments, resisting desiccation and UV stress and improving competition with other microbes (Fox and Howlett, 2008). These secondary metabolites play important roles during various physiological processes under different conditions and stress (Costa, 2012; Fox and Howlett, 2008). Secondary metabolites have broad spectrum of application fields covering agriculture, food, and pharmaceutical industry (Keller *et al.*, 2005; Bills *et al.*, 2017). Importantly, the fungal secondary metabolites have immense potential for drug discovery including antibiotics (Aly *et al.*, 2011; Devi *et al.*, 2020). Some fungi are considered 'medicinal' because their secondary metabolites are being usage in systems of traditional medicine to treat human ailments (Lenzi *et al.*, 2018). There is a long array of SMs that are reported from different

fungal species (Keller *et al.,* 2005; Bills *et al.,* 2017). With the application of new and advanced multi-omic sciences (such as comparative genomics, transcriptomics, proteomics, and metabolomics) and bioinformatics (massive data analysis), the pool of novel secondary metabolites is gradually expanding in numerous species (Tong *et al.,* 2019).

Further, the results obtained through these techniques explain the actual behaviours of the fungal cells by providing data on the biological, cellular, and molecular functions, which help in the better understanding of interactions between environmental factors, genetic variants, genetic expression patterns, and changes in the concentration of metabolites. Therefore, the persistence of secondary metabolites and its diversity in evolution implies a competitive benefit in nature (Vining, 2007).

Fungal secondary metabolites exhibit a staggering variation and diversities in its chemical structures and biological activities (Molnar *et al.,* 2010; Bills and Gloer, 2017). There are four basic chemical groups of fungal secondary metabolites: polyketides, terpenoids, shikimic acid derived compounds, and non-ribosomal peptides (Keller, 2019). The biosynthetic pathways of secondary metabolites share a number of key characteristics (Bills and Gloer, 2017). Generally, secondary metabolites are synthesized from the metabolism of substrates from primary metabolic pathways, among which acetyl-CoA stands out as the precursor of polyketides and terpenoids. Biosynthetic pathway of each secondary metabolites starts with a characteristic type of enzyme. Specific tailoring enzymes regulate the complete pathways by introducing additional modifications to the molecules. The structural features of secondary metabolites are an important aspect to understand the relationship between their molecular structures and biological or pharmacological activities.

In the present study, attempts have been made to evaluate the physicochemical properties of secondary metabolites that are important for the success and survival of opportunistic fungi. *Aspergillus fumigatus* is taken as model fungal species in this study, which is ubiquitous in various environments. *A. fumigatus* is one of the most common and medicinally important saprophytic fungal species (Latgé, 1999). Yet it is also equally adept as a serious opportunistic pathogen which causes pulmonary invasive aspergillosis. *A. fumigatus* has an arsenal of secondary metabolites that impact on disease development and pathogenesis (Bignell *et al.,* 2016; Raffa *et al.,* 2019).

Some secondary metabolites combat the host immune system by affecting immune cell function or by shielding the fungus against host attack, whereas others allow the fungus to acquire essential, scarce cofactors. The structural and physiochemical features present in secondary metabolites are accountable for delivering a variety of characteristics including therapeutic applications, the solubility, and stability of the molecules (Sharma *et al.,* 2022). Hence the knowledge about characteristic physiochemical properties of secondary metabolites will be useful to understand the relations between their molecular structures and biological activities that are attributed to being responsible for arousing a target biological effect in *A. fumigatus*.

Materials and Methods

The 2D structures of secondary metabolites were obtained from standard chemical database 'PubChem' (https://pubchem.ncbi.nlm.nih.gov/) (Kim *et al.,* 2021) by mapping to chemical identifiers. Apart from structure information, the canonical "Simplified Molecular Input Line Entry System" (SMILES) of the compounds were also generated from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database.

The basic physicochemical properties of the secondary metabolites were computed using SwissADME (http://www.swissadme.ch/) (Daina *et al.,* 2017). To assess the druglikeness of the

secondary metabolites, we have computed multiple scoring schemes and properties namely, Lipinski's rule of five (RO5), Ghose filter, Number of Leadlikeness violations and weighted quantitative estimate of drug-likeness (QEDw). The assessment of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties were predicted by SwissADME.

Putative protein targets of secondary metabolites were identified by the recently described method by Gu *et al.,* (2020) and Fawzi Mahomoodally *et al.,* (2020). The canonical SMILES of the secondary metabolites were then processed by Swiss Target Prediction (http://www.swisstargetprediction.ch/) (Gfeller *et al.,* 2014) webserver for predicting the putative targets.

Results and Discussion

Here I targeted to evaluate and delineate the physicochemical properties of specific secondary metabolites (Table 1) that are produced by *A. fumigatus,* and help into its success. Such as Dihydroxynapthalene melanin, Gliotoxin, Endocrocin, Fumagillin, and Fumigaclavines helps to combat the immune system during pathogenesis (Table 1; SM1 to SM5). While Siderophores, Hexadehydroastechrome, and Xanthocillins are required to compete in the environment and the host (Table 1; SM6 to SM8). Secondary metabolites such as Trypacidin, Helvolic acid, Fumiquinazolines, Fumitremorgins, Pyripyropene A, Pseurotin, Neosartoricin, Fumisoquin, and Nidulanin A regulate the key aspects of essential micronutrients homeostasis (Table 1; SM9 to SM17). The chemical names of these secondary metabolites were mapped to chemical identifiers employed by standard chemical databases 'PubChem' database. The 2D chemical structures (Figure 1) and SMILE formulae (Table 1) of these secondary metabolites were manually retrieved from 'PubChem'. These SMILE formulae were further used as input for the evaluation of physiochemical properties of these secondary metabolites.

Evaluation and Assessment of Drug-likeness Properties

Drug-likeness analysis is very a crucial and important step in the early stage of drug discovery. SwissADME was used to calculate Drug-likeness properties like logP, MW, number of hydrogen-bond acceptors (HBA), number of hydrogen-bond donors (HBD), MLOGP, WLOGP, MR, and number of atoms for each secondary metabolite by applying Lipinski's rule of five (RO5) and Ghosh filter. As stated in Lipinski's rule of five (RO5), a drug-like compound must have a molecular weight (MW) $\leq$ 500 Da, hydrogen bond donor (HBD's) $\leq$ 5, hydrogen bond acceptor (HBAs) $\leq$ 10 and (log P) $\leq$ 5 with only one violation allowed (Lipinski 2004). Out of 17, 13 secondary metabolites passed Lipinski's and Ghosh Filter without any violations and thus showed drug-likeness properties. The results of the drug-likeness of the respective secondary metabolites are shown in Table 2.

An analysis of the bioavailability RADAR (Figure 2) gives the bioavailability properties of the secondary metabolites. The pink area in the RADAR plot shows the most favourable zone for each of the bioavailability properties. It is clear in Table 2 that all the selected secondary metabolites fulfilled the recommended size ($\leq$ 500 g/mol) by Lipinski for good drug candidates, except SM7, SM10, SM13 and SM17 for which the obtained size are 1113.07, 568.70, 583.63 and 603.75 g/mol, respectively.

Total Polarity Surface Area (TPSA) was used to assess the polarity (POLAR) of secondary metabolites. Except SM2, SM3, SM7, SM13, SM14, SM15 and SM17, the TPSA values of other selected secondary metabolites within the acceptable range of 20 – 130 Å2 (Table 2). The total number of rotatable bonds in a molecule was used to evaluate the flexibility (FLEX) property. Except SM4, SM7 and SM17, all the targeted secondary metabolites are having tolerable number of rotatable bonds (tolerable range $\leq$ 9) (Table 2). Lipophilicity (LIPO) was evaluated using XLOGP3.

Table.1 SMILE code of the targeted secondary metabolites.

S No.	Secondary metabolites	SMILE Code
SM1	Dihydroxynapthalene melanin	OC1=CC=CC2=C(C=CC=C12)O
SM2	Gliotoxin	CN1C(=O)[C@]23CC4=CC=C[C@@H]([C@H]4N2C(=O)[C@]1(SS3)CO)O
SM3	Endocrocin	CC1=CC2=C(C(=C1C(=O)O)O)C(=O)C3=C(C2=O)C=C(C=C3O)O
SM4	Fumagillin	CC(=CC[C@@H]1[C@@](O1)(C)[C@H]2[C@@H]([C@@H](CC[C@]23CO3)OC(=O)/C=C/C=C/C=C/C=C/C(=O)O)OC)C
SM5	Fumigaclavines C	C=CC(c1[nH]c2c3c1C[C@H]1N(C)C[C@@H]([C@@H]([C@@H]1c3ccc2)OC(=O)C)C)(C)C
SM6	Siderophores	CN1[C@@H](CS[C@@H]1[C@H]2CSC(=N2)C3=CC=CC=C3O)C(=O)O
SM7	Hexadehydroastechrome	CC1=NC(=C(N(C1=[OH+])O)CC2=CNC3=C(C=CC=C23)/C=C/C(=C)C)OC.CC1=NC(=C(N(C1=[OH+])O)CC2=CNC3=C(C=CC=C23)/C=C/C(=C)C)OC.CC1=NC(=C(N(C1=[OH+])O)CC2=CNC3=C(C=CC=C23)/C=C/C(=C)C)OC.[Fe]
SM8	Xanthocillins	[C-]#[N+]/C(=C\C1=CC=C(C=C1)O)/C(=C/C2=CC=C(C=C2)O)/[N+]#[C-]
SM9	Trypacidin	CC1=CC2=C(C(=C1)OC)C(=O)C3(O2)C(=CC(=O)C=C3OC)C(=O)OC
SM10	Helvolic acid	C[C@H]1[C@@H]2[C@@H](C(=O)[C@]3([C@H]([C@]2(C=CC1=O)C)CC[C@@H]\4[C@@]3(C[C@@H](/C4=C(/CCC=C(C)C)\C(=O)O)OC(=O)C)C)C)OC(=O)C
SM11	Fumiquinazolines	C[C@H]1C2=NC3=CC=CC=C3C(=O)N2[C@@H](C(=O)N1)CC4=CNC5=CC=CC=C54
SM12	Fumitremorgins	CC(=CCN1C2=C(C=CC(=C2)OC)C3=C1[C@@H](N4C(=O)[C@@H]5CCCN5C(=O)[C@@]4([C@H]3O)O)C=C(C)C)C
SM13	Pyripyropene A	CC(=O)OC[C@@]1([C@H](CC[C@]2([C@H]1C[C@@H]([C@@]3([C@@H]2[C@H](C4=C(O3)C=C(OC4=O)C5=CN=CC=C5)O)C)OC(=O)C)C)OC(=O)C)C
SM14	Pseurotin	CC/C=C\[C@@H]([C@@H](C1=C(C(=O)[C@@]2(O1)[C@H]([C@@](NC2=O)(C(=O)C3=CC=CC=C3)OC)O)C)O)O
SM15	Neosartoricin	CC(=CCC1=C2C=C(C=C(C2=C(C3=C1C[C@]([C@@H](C3=O)OC(=O)C)(C/C(=C/C(=O)C)/O)O)O)O)O)C
SM16	Fumisoquin	C1[C@@H]([C@@H]2[C@@H](C3=C(CN2C(=O)[C@H]1[NH3+])C(=C(C=C3)O)O)O)O
SM17	Nidulanin A	CC(C)[C@@H]1C(=O)N[C@H](C(=O)N[C@H](C(=O)N[C@H](C(=O)N1)CC2=CC=CC=C2)CC(=O)C3=CC=CC=C3NC(C)(C)C=C)C(C)C

Table.2 Drug-likeness properties of secondary metabolites

S. No.	Secondary Metabolites	A	B	C	D	E	F	G	H	I	J	K
SM1	Dihydroxynapthalene melanin	160.17	0	0	2	47.99	40.46	1.94	-2.67	0	0	0.55
SM2	Gliotoxin	326.39	0.54	1	4	86.8	131.68	-0.72	-1.34	0	1	0.55
SM3	Endocrocin	314.25	0.06	1	7	77.74	132.13	2.8	-3.87	0	0	0.56
SM4	Fumagillin	458.54	0.54	11	7	124.77	97.89	3.96	-4.45	0	0	0.56
SM5	Fumigaclavines C	366.5	0.52	4	3	114.16	45.33	4.74	-5.08	0	0	0.55
SM6	Siderophores	324.42	0.43	3	5	93.63	123.73	-0.35	-1.64	0	0	0.55
SM7	Hexadehydroastechrome	1113.07	0.2	15	12	311.87	249.9	9.74	-12.31	4	4	0.17
SM8	Xanthocillins	288.3	0	3	4	83.64	40.46	3.15	-3.82	0	0	0.55
SM9	Trypacidin	344.32	0.28	4	7	85.67	88.13	1.51	-2.84	0	0	0.56
SM10	Helvolic acid	568.7	0.67	8	8	154.83	124.04	5.12	-6.06	1	3	0.56
SM11	Fumiquinazolines	358.39	0.19	2	3	107.8	79.78	2.54	-4.05	0	0	0.55
SM12	Fumitremorgins	479.57	0.48	4	5	140.82	95.24	2.65	-4.41	0	1	0.55
SM13	Pyripyropene A	583.63	0.58	8	11	149.19	151.46	2.46	-4.69	2	3	0.17
SM14	Pseurotin	431.44	0.41	7	8	111.61	142.39	0.54	-2.54	0	0	0.56
SM15	Neosartoricin	484.5	0.35	7	9	129.02	161.59	3.98	-5.1	0	1	0.11
SM16	Fumisoquin	281.28	0.46	0	5	73.53	128.87	-1.87	-0.63	0	1	0.55
SM17	Nidulanin A	603.75	0.44	10	5	186.88	145.5	5.22	-6.41	1	3	0.55

Details of Columns

A: MW
B: Fraction Csp3
C: No. of Rotatable bonds
D: No. of H-bond acceptors
E: MR
F: TPSA
G:XLOGP3
H:ESOL Log S
I:No. of Lipinski violations
J:No. of Ghose violations
K:Bioavailability Score

Table.3 ADME properties of secondary metabolites

S. No.	Secondary Metabolites	A	B	C	D	E	F	G	H	I
SM1	Dihydroxynapthalene melanin	High	Yes	No	Yes	No	No	No	No	-5.9
SM2	Gliotoxin	High	No	Yes	No	No	No	No	No	-8.8
SM3	Endocrocin	High	No	No	No	No	No	No	Yes	-6.23
SM4	Fumagillin	High	No	No	No	No	Yes	No	Yes	-6.29
SM5	Fumigaclavines C	High	Yes	No	No	Yes	Yes	Yes	Yes	-5.17
SM6	Siderophores	High	No	No	No	No	No	No	No	-8.53
SM7	Hexadehydroastechrome	Low	No	Yes	No	No	No	No	No	-6.17
SM8	Xanthocillins	High	Yes	No	Yes	No	No	No	Yes	-5.82
SM9	Trypacidin	High	No	No	No	No	Yes	No	No	-7.33
SM10	Helvolic acid	Low	No	Yes	No	No	No	No	No	-6.13
SM11	Fumiquinazolines	High	No	Yes	No	Yes	Yes	Yes	No	-6.68
SM12	Fumitremorgins	High	No	Yes	No	No	No	Yes	No	-7.34
SM13	Pyripyropene A	Low	No	Yes	No	No	No	No	Yes	-8.11
SM14	Pseurotin	Low	No	Yes	No	No	No	No	No	-8.55
SM15	Neosartoricin	Low	No	Yes	No	No	Yes	No	Yes	-6.43
SM16	Fumisoquin	Low	No	No	No	No	No	No	No	-9.34
SM17	Nidulanin A	Low	No	Yes	No	No	No	No	Yes	-6.28

Details of columns

A: GI absorption
B: BBB permeant
C: Pgp substrate
D: CYP1A2 inhibitor
E: CYP2C19 inhibitor
F: CYP2C9 inhibitor
G: CYP2D6 inhibitor
H: CYP3A4 inhibitor
I: log Kp (cm/s)

Table.4 Predicted targets of secondary metabolites

S No.	Secondary metabolites	Target	Uniprot ID	Target Class	Probability*
SM1	Dihydroxynapthalene melanin	Indoleamine 2,3-dioxygenase	P14902	Enzyme	0.795428112
SM2	Gliotoxin				
SM3	Endocrocin	Alpha-ketoglutarate- dioxygenase FTO	Q9C0B1	Oxidoreductase	0.176593625
SM4	Fumagillin	Methionine aminopeptidase 2	P50579	Protease	1
SM5	Fumigaclavines C	Serotonin 2b (5-HT2b) receptor	P41595	Family A G protein-coupled receptor	0.361228277
SM6	Siderophores				
SM7	Hexadehydroastechrome	Dihydroorotate dehydrogenase	Q02127	Oxidoreductase	0.109339753
SM8	Xanthocillins	Histone deacetylase 5	Q9UQL6	Eraser	0.111501865
SM9	Trypacidin	Matrix metalloproteinase 9	P14780	Protease	0
SM10	Helvolic acid	Cytochrome P450 19A1	P11511	Cytochrome P450	0.074392272
SM11	Fumiquinazolines	Nitric-oxide synthase, brain	P29475	Enzyme	0.113285953
SM12	Fumitremorgins	ADAM17	P78536	Protease	0.110612204
SM13	Pyripyropene A	Acyl coenzyme A	P35610	Enzyme	1
SM14	Pseurotin				
SM15	Neosartoricin	Protein kinase C gamma	P05129	Kinase	0.110612204
SM16	Fumisoquin	Purine nucleoside phosphorylase	P00491	Enzyme	0.100578902
SM17	Nidulanin A	Neurokinin 2 receptor	P21452	Family A G protein-coupled receptor	0.074564954

Fig.1 (A to Q). 2-D structures of secondary metabolites Dihydroxynapthalene melanin, Gliotoxin, Endocrocin, Fumagillin, Fumigaclavines, Siderophores, Hexadehydroastechrome, Xanthocillins, Trypacidin, Helvolic acid, Fumiquinazolines, Fumitremorgins, Pyripyropene A, Pseurotin, Neosartoricin, Fumisoquin, and Nidulanin A, respectively.

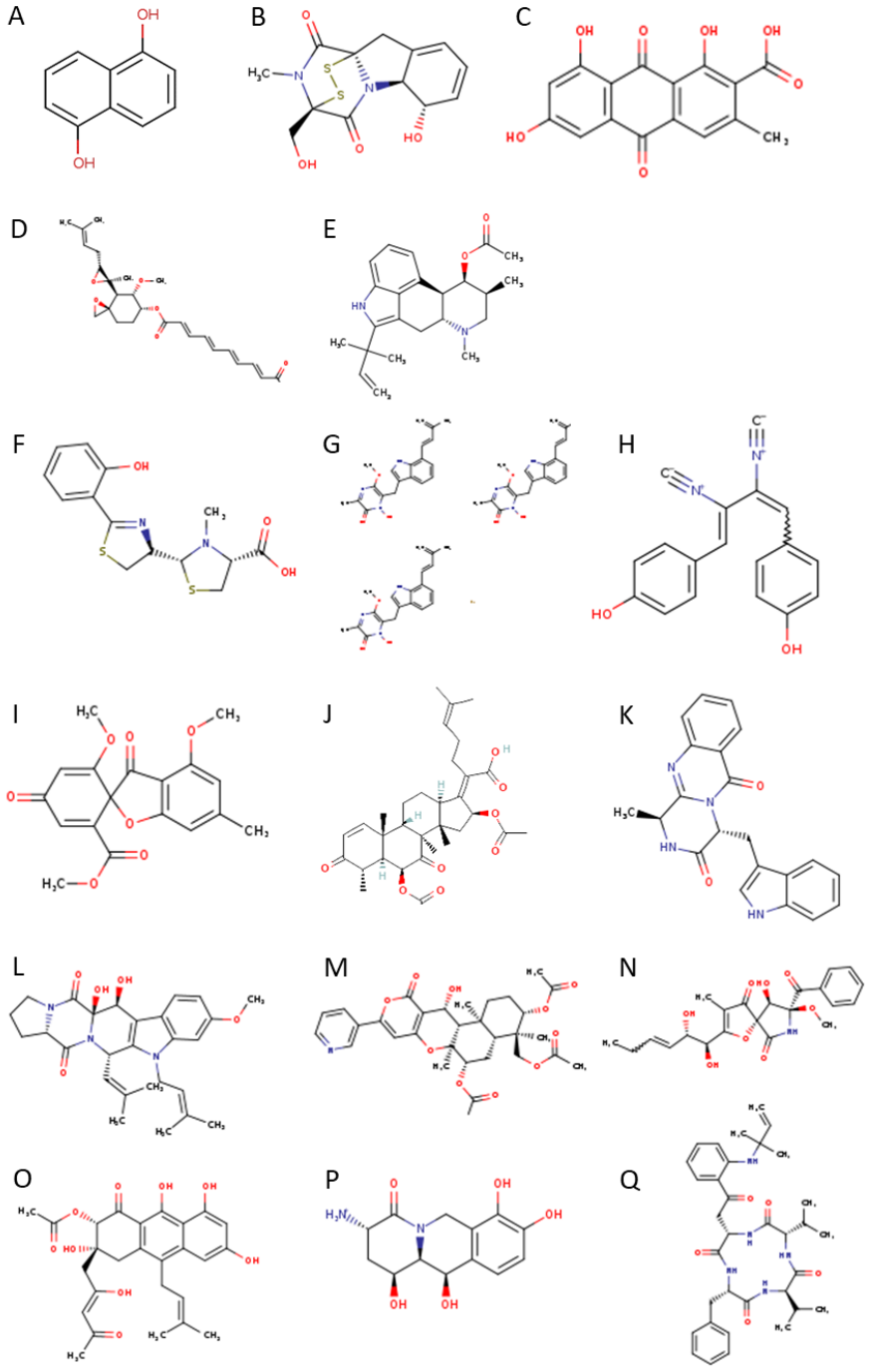
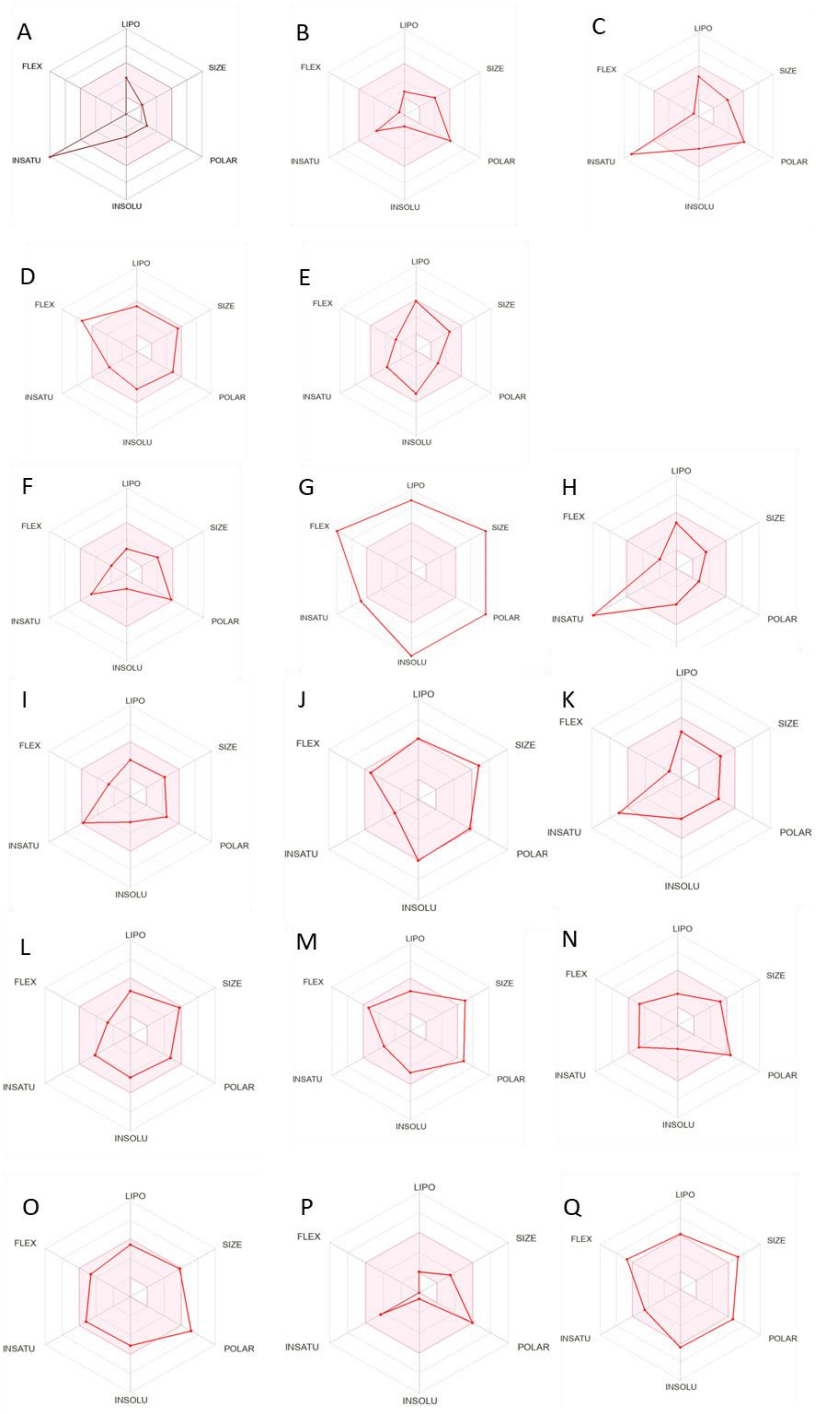


Fig.2 (A to Q). Bioavailability Radar Plot of secondary metabolites Dihydroxynapthalene melanin, Gliotoxin, Endocrocin, Fumagillin, Fumigaclavines, Siderophores, Hexadehydroastechrome, Xanthocillins, Trypacidin, Helvolic acid, Fumiquinazolines, Fumitremorgins, Pyripyropene A, Pseurotin, Neosartoricin, Fumisoquin, and Nidulanin A, respectively. The pink area shows the optimal range for each property (Lipophilicity: XLOGP3 between − 0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 Å2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds)



Lipophilicity shows the permeability of secondary metabolites across the cell membrane (Potts and Guy, 1992; Rutkowska *et al.,* 2013). The XLOGP3 value for most of the targeted secondary metabolites fall within the recommended range from – 0.7 to + 5.0, except SM2, SM7, SM10, SM16 and SM17, which suggest a good permeability and absorption across the cell membrane (Table 2). Further, insolubility is another important parameter influencing absorption of secondary metabolites in any formulation process. Insolubility (INSOLU) was evaluated using ESOL (log S) for which the recommended ranges are 'Insoluble < -10 < Poorly < -6 < Moderately <-4< Soluble < -2 Very < 0 < Highly'. The ESOL (log S) value suggest that most of the targeted secondary metabolites are either 'soluble' or 'moderately soluble' (Table 2). Interestingly SM7 is predicted as 'Insoluble' (ESOL (log S): '-12.31'), which may be due to its high molecular weight.

The Unsaturation (INSATU) parameter was determined using 'Fraction Csp3' for which the recommended range is between 0.5 to 1. Interestingly the predicted value of 'Fraction Csp3' for most of the secondary metabolites were below 0.5 (Table 2). Exceptionally SM1 and SM8 were predicted 0 'Fraction Csp3' value. Most of the selected secondary metabolites are predicted to have the bioavailability score either 0.55 or 0.56 (Table 2) means these metabolites are possessing outstanding oral-bioavailability properties. Exceptionally, SM15 have the bioavailability score either 0.11 which is lower than the standard value 0.17 (Table 2).

Evaluation and Assessment of absorption, distribution, metabolism, excretion and toxicity (ADMET) Properties

As observed in Table 3, the analyses of pharmacokinetics parameters of secondary metabolites suggest that SM1, SM2, SM3, SM4, SM5, SM6, SM8, SM9, SM11 and SM12 have high propensities for gastrointestinal (GI) absorption, thus these secondary metabolites will easily be absorbed in the human intestine. Interestingly most of the targeted secondary metabolites are predicted to have no ability to cross the bloodbrain barrier (BBB permeant) (Table 3) suggesting the absence of effects on the central nervous system (CNS). Microsomal enzymes such as Cytochrome P450 inhibitors catalyse reactions involved in metabolic activities of the drug (Rendic and Carlo 1997). Potential for Cytochrome P450 inhibition were used to assess the metabolic activities of the secondary metabolites.

The observed data (in Table 3) suggest that almost all secondary metabolites are non-inhibitors of all the CYP450 inhibitors. Prediction of skin permeability coefficient (Kp) of the secondary metabolites was done as described by Potts and Guy (Potts and Guy, 1992). The log *K*p were predicted between − 5.17 to − 9.34 cm/s (Table 3), while the more negative log *K*p, the less skin permeant is the compounds.

Prediction of Putative Pharmacologic Targets

Secondary metabolites were further evaluated for the identification of the putative target protein in human proteins by network pharmacology methods. 'Swiss Target Prediction' online tool was used to calculate the potential targets. The result showed only SM1, SM4 and SM13 have high probability (≥8) to target human protein Indoleamine 2,3-dioxygenase, Methionine aminopeptidase 2, and Acyl coenzyme A: cholesterol acyltransferase 1, respectively (Table 4). These metabolites also interact with the multiple protein targets which showed their efficacy towards the pharmacological activity. Rest all are predicted with very low probability (Table 4). These results corroborate the molecular docking analysis for further prospects.

Physicochemical properties of secondary metabolites are important parameters during its biotechnological applications. Prior to calculate the potential of any secondary metabolites, its physicochemical properties must be assessed. The physicochemical properties are parameters that

points the different ADME attributes, such as solubility, permeability, and oral absorption. The *in-silico* evaluation of ADME, druglikeness and pharmacokinetics of these secondary metabolites display the relative the viability of the Dihydroxynapthalene melanin, Gliotoxin, Endocrocin, Fumagillin, Fumigaclavines C, Siderophores, Xanthocillins, Trypacidin, Pyripyropene A, Fumisoquin. Their active pharmacological principle may act as an oral drug with low toxic risk via the topical route. The findings from this analysis provide the basis for the future prospects of these important secondary metabolites.

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