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Druggability of lead compounds from turmeric (*Curcuma longa*)

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ABSTRACT

Curcumin (diferuloylmethane), the main bioactive component of turmeric, has been proved to have a wide spectrum of biological actions through several pharmacological studies. However, cheminformatics approaches are seldom used in these studies. *In silico* approaches can help in identifying better drug candidates that are safe, besides cutting down the high costs. In this study, *in silico* tools were applied to chemical compounds in turmeric for the first time to predict their biological activities and druggability. The druggability of these compounds was checked by using the Lipinski's scoring functions such as Log P, molecular weight, number of hydrogen bond donors and number of hydrogen bond acceptors. The results of these *in silico* studies indicate that, in contrast to curcumin, several other compounds in turmeric exhibit better activities which have to be confirmed by both pharmacological and clinical studies.

Key words: Druggability, turmeric, virtual screening, PASS prediction.

INTRODUCTION

Turmeric (*Curcuma domestica* Syn., *C. longa*) is extensively used as a spice, food preservative and colouring material in India, China and South East Asia [4]. Traditionally many medicinal properties are attributed to this spice. Turmeric has been used since ancient times in Ayurveda, the age-old system of health care in India. For the last few decades, extensive work has been done to establish the biological activities of turmeric and its extracts. However, no druggability studies have been carried out on any compounds other than curcumin. Curcumin, a major chemical constituent of turmeric, has a wide spectrum of biological properties which have been compiled and reviewed by several workers [4]. Even though the crude extracts has numerous medicinal applications, clinical applications can be made only after extensive research on its bioactivity, mechanism of action, pharmacotherapeutics and toxicity studies.

Drug discovery projects experience very high failure rates. By going back to nature, one could overcome these failure rates and it is as an invaluable source of inspiration for drug discovery. Scientific evidence underpins the pharmacological activity of several herbs which possess a number of novel therapeutic drug leads [3, 12]. The global market for herbal products may be around US$5 trillion by 2050 [13]. The properties of drug-like molecules are well studied and cover a wide range of sizes and physicochemical properties [11, 18]. The slowness of conventional methods for investigation of plants limits enthusiasm in using them in the pharmaceutical industry [12]. Virtual screening is acknowledged as the initial means for identifying hit compounds that will be eventually transformed to leads or drug candidates [1, 16]. Structure information is increasingly used in the drug design process and has contributed significantly to the discovery of several marketed drugs [2, 6, 7, 14]. Furthermore, it is well known that *in silico* approaches are comparatively cheaper than *in vivo* and *in vitro* screenings.

Spices possess several efficacious compounds that are absorbed, distributed to the correct area, metabolized and excreted effectively. However, the cheminformatics approach is currently not employed in any of the spices to study the medicinal properties traditionally attributed to them. Such a study of active principles of spices may minimize the side-effects commonly seen with the drugs available in the market. In the present study, turmeric was taken as a model and different compounds in it were analyzed virtually using *in silico* tools to study their drug or lead-likeness. The results of this study will help chemists in prioritizing compound-selection depending on the nature of the application.

MATERIALS AND METHODS

Structure collection and database screening

The structures of the chemical compounds from turmeric, collected from the NCI and the PubChem databases, are drawn using ACD/Chemsketch (Table 1). The structures were converted into SMILES notation to compare with the known active chemical compounds existing in the databases. This idea can be used for screening molecular databases for similar modes of actions on the one hand, or for screening one single compound for potential side-effects (reversed screening) on the other hand [9].

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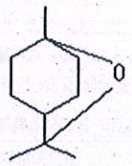
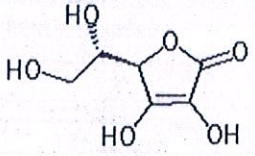
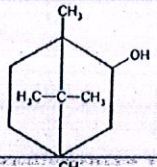
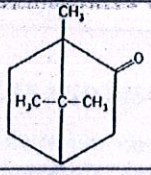
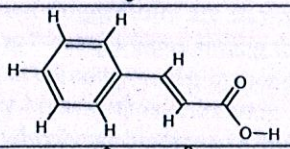
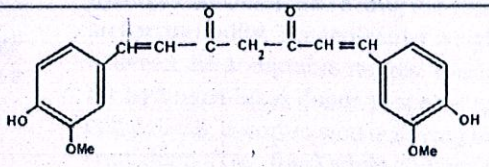
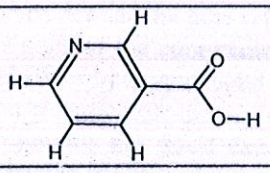
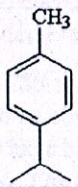
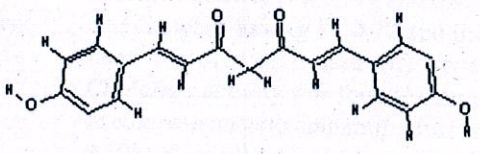
1. Structure and molecular formula of selected compounds from turmeric

SN	Compound	Molecular Formula	Structure
1	1,8 cineole	$C_{10}H_{18}O$	
2	Ascorbic acid	$C_6H_8O_6$	
3	Borneol	$C_{10}H_{18}O$	
4	Camphor	$C_{10}H_{16}O$	
5	Cinnamic acid	$C_9H_8O_2$	
6	Curcumin	$C_{21}H_{20}O_6$	
7	Niacin	$C_6H_5NO_2$	
8	P-Cymene	$C_{10}H_{14}$	
9	Bisdemethoxycurcumin	$C_{19}H_{16}O_4$	

Druggability check

The compounds were checked for their druggability using Lipinski's scoring functions [11]. The scoring function used to assess druggability of the compounds is shown in Table 2. The number of hydrogen bond donors refer to OH and NH groups, whereas hydrogen bond acceptors refer to O and N atoms according to Lipinski's definition; logP is the log of the octanol/water partition coefficient (including implicit hydrogen). LogP was chosen as a simple model for phospholipid-membrane. Its values represent the hydrophobic binding of a drug to a receptor, its water solubility and permeability. However, it shows a serious shortcoming in predicting BBB (blood brain barrier) or skin penetration. Typical values range from -3 (very hydrophilic) to +7 (very hydrophobic) and most drugs have logP values in the range of 2-4. For example, the experimental logP values are: 2.0 (CNS penetration), 1.8 (oral absorption), 1.3 (intestinal absorption), 1.3 (colonic absorption), 5.5 (sub-lingual absorption), and 2.6 (percutaneous). Lipinski used Hansch and Leo's logP definition (ClogP-Daylight/Biobyte) which corresponds to a fragment-based method.

Table 2. Lipinski's scoring function

Property filters	Definition	Minimum	Cut-off	Maximum
No: of hydrogen bond donors	Hdon	0	5	6
No: of hydrogen bond acceptors	Hacc	0	10	11
Molecular Weight	MW	100	500	600
Log P	xlogp	-2	5	6
Predicted activity	Pa	<0.5	0.7	>0.7

Activity prediction

The compounds were also checked for their possible biological activities by using PASS (Prediction of Activity Spectra for Substances), which predicts more than 300 biological activities and biochemical mechanisms on the basis of the structural formula of a substance. This may be efficiently used to find new targets (mechanisms) for some ligands and conversely, to reveal new ligands for some biological targets. A www server for the online prediction of the biological activity spectra of substances has been used [8]. (Availability: http://www.ibmh.msk.su/PASS). The Biological Activity Spectrum (BAS) of a compound represents the complex of biological effects- physiological and biochemical mechanisms of action, specific toxicity (mutagenicity, carcinogenicity, teratogenicity and embryotoxicity) which can be revealed in compound's interaction with biological system.

Activity Scoring

The scoring functions used to check the biologically active substances are given below.

If predicted activity (Pa) > 0.7, the substance is v likely to exhibit the activity in experiment and the chanc the substance to be the analogue of a known pharmaceuti agent is also very high.

If 0.5<Pa<0.7, the substance is likely to exhibit activity in experiment and the probability is less, and substance is unlike to be a known pharmaceutical agent.

If Pa <0.5, the substance is unlikely to exhibit the activ in experiment. However, if the presence of this activity confirmed in the experiment, the substance might have a n chemical activity.

RESULTS AND DISCUSSION

The results on screening the chemical compounds fo their druggability are shown in the Figure-1 (A and B). Th log P comparisons among the selected compounds suggested that the compound p-cymene has a better log P (4.13) followed by bisdemethoxycurcumin and curcumin. It represents the hydrophobic binding of a drug to a receptor, its water solubility and permeability. The molecular weights of all compounds are between the acceptable ranges. Based on the Lipinski's rule for hydrogen bond donor property, among the nine selected compounds, ascorbic acid is having the highest number of H-bond donors (ie., four) while curcumin has only three H-bond donors. Among the nine selected compounds it is also noted that none of the compounds satisfied the cut-off value for Lipinski's hydrogen bond acceptor property. The results clearly indicated that in turmeric, none of the studied compounds are good candidates for developing drugs. Compared to curcumin, compounds like p-cymene, ascorbic acid and bisdemethoxycurcumin are better candidates.

The PASS analysis yielded 51 predicted activities for the selected nine compounds from turmeric (Table 3). Borneol and camphor have high analeptic activities, Pa 0.907 and 0.973, respectively. They also have the maximum respiratory analeptic activity (Pa 0.774 and 0.927, respectively). Borneol and camphor having Pa 0.72 and 0.717, respectively, can be used for prostatic (benign) hyperplasia treatment too. Choleretic activity was found better for 1, 8 cineole (Pa 0.94), in comparison with cinnamic acid (Pa 0.75) and curcumin (Pa 0.898). Convulsant activity was present in camphor (Pa 0.859) as well as p-cymene (Pa 0.743). They are also having high oxidoreductase inhibitor activity, Pa 0.702 and 0.741,

Table 3. List of PASS predicted biological activities for the druggable compounds from turmeric

	Biological activities	1,8 Cineole	Ascorbic acid	Borneol	Camphor	Cinnamic acid	Curcumin	Niacin	P-Cymene	Bisdesmethoxy curcumin
		<< Pa Values >>								
1	Acute neurologic disorders treatment	-	0.722	-	-	-	-	-	-	-
2	ADP ribose polymerase inhibitor	-	-	-	-	-	-	0.791	-	-
3	Analeptic	-	-	0.907	0.973	-	-	-	-	-
4	Analgesic	0.726	-	-	-	-	-	-	-	-
5	Analgesic, non-opioid	0.863	-	-	-	-	-	-	-	-
6	Anticataract	-	0.955	-	-	-	-	-	-	-
7	Antidyskinetic	0.717	-	-	-	-	-	-	-	-
8	Antihypercholesterolemic	-	-	-	-	-	0.819	-	-	-
9	Antiinflammatory	-	-	-	-	-	0.719	-	-	0.927
10	Antiischemic	-	0.908	-	-	-	-	-	-	-
11	Antioxidant	-	0.891	-	-	-	0.758	-	-	-
12	Antitoxic	-	-	-	-	-	0.799	-	-	-
13	Apoptosis agonist	-	-	-	-	0.822	0.8	0.732	-	0.705
14	Arrhythmogenic	0.806	-	-	0.911	-	-	-	-	-
15	Atherosclerosis treatment	-	-	-	-	-	0.704	-	-	0.726
16	Cardiovascular analeptic	-		0.927	-	-	-	0.848	-	-
17	Choleretic	0.94	-	-	-	0.75	0.898	-	-	-
18	Cholesterol antagonist	0.956	-	-	-	-	-	-	-	-
19	Cholesterol synthesis inhibitor	-	-	-	-	0.836	-	-	-	-
20	Convulsant	-	-	-	0.859	-	-	-	0.743	-

21	Fibrinogen receptor antagonist	-	-	-	-	0.813	-	-	-	-
22	Fibrinolytic	-	-	-	-	-	-	-	0.754	-
23	GABA C receptor agonist	-	-	-	-	0.854	-	-	-	-
24	Hepatic disorders treatment	0.818	-	-	-	-	-	-	-	-
25	Hepatoprotectant	0.816	-	-	-	-	-	-	-	-
26	Inflammatory Bowel disease treatment	-	-	-	-	0.806	-	-	-	-
27	Interleukin 1 antagonist	-	-	-	-	-	0.712	-	-	-
28	Lipid metabolism regulator	-	-	-	-	0.707	-	-	-	-
29	Lipid peroxidase inhibitor	-	0.863	-	-	-	-	-	-	-
30	5 Lipoxygenase inhibitor	-	-	-	-	-	0.79	-	-	-
31	Male reproductive disfunction treatment	-	-	-	0.773	-	-	-	-	-
32	Melanin inhibitor	-	-	-	-	-	0.724	-	-	0.701
33	Membrane integrity agonist	-	-	-	-	0.945	0.841	-	-	0.712
34	Membrane permeability inhibitor	-	-	-	-	-	-	-	0.726	-
35	Multiple sclerosis treatment	0.757	-	-	-	-	-	-	-	-
36	Myocardial ischemia treatment	-	0.929	-	-	0.728	-	-	-	-
37	Neuroprotector	-	0.911	-	-	-	-	-	-	-
38	Oxidoreductase inhibitor	-	-	-	0.702	-	-	-	-	-
39	Oxygen scavenger	-	0.741	-	-	-	-	-	0.741	-
40	Phosphatase inhibitor	-	0.772	0.862	0.805	-	-	-	-	-
41	Plasminogen activator stimulant	-	0.705	-	-	-	-	-	0.839	-
42	Prostatic (benign) hyperplasia treatment	-	-	0.721	0.717	-	-	-	-	-
43	Pulmonary hypertension treatment	-	-	-	-	-	-	-	-	-
44	Reductant	-	0.791	-	-	-	-	-	0.808	-
45	Respiratory analeptic	-	-	0.774	0.927	-	0.862	-	-	-
46	RNA polymerase RNA directed inhibitor	-	-	-	0.792	-	-	-	-	-
47	Sigma receptor agonist	-	-	-	-	0.807	-	-	-	-
48	Tocolytic	-	-	-	0.711	-	-	-	-	-
49	Tyrosine phosphatase inhibitor	-	-	-	-	0.949	0.792	-	-	-
50	Ulcerogenic	-	-	-	-	-	0.966	-	-	-
51	Vascular (periferal) disease treatment	-	-	-	-	0.713	-	-	-	0.705

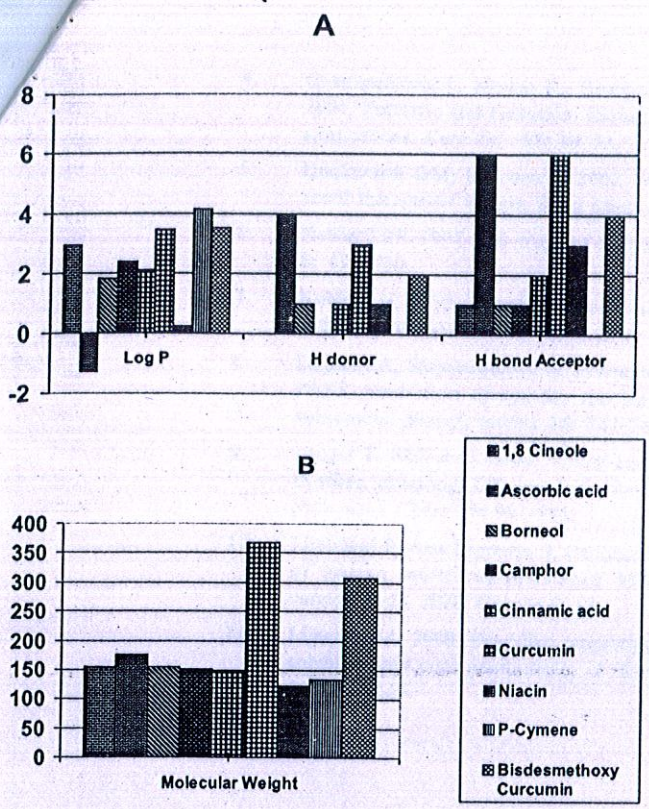


Fig. 1. Lipinski's druggability check in turmeric compounds A. Log P, Hydrogen bond donor and acceptor; B. Molecular Weight

espectively. Phosphatase inhibitor activities are common for scorbic acid (Pa 0.772), borneol (Pa 0.862), camphor (Pa 0.805) nd p-cymene (Pa 0.839). Tyrosine phosphatase inhibitor ctivity was found better for cinnamic acid (Pa 0.949) in omparison with curcumin (Pa 0.792). It is interesting to note hat anti-inflammatory activity is more for isdemethoxycurcumin (Pa 0.927) in comparison with curcumin Pa 0.719). This also correlates that bisdemethoxycurcumin is ıe most active of the curcuminoids present in turmeric, in oncurrence with Limtrakul *et al.* [10]. In contrast to anti-ıflammatory activity, activities like apoptosis agonist is little reater for curcumin (Pa 0.8) rather than isdemethoxycurcumin (Pa 0.705). Besides curcumin, cinnamic :id and niacin also contributes apoptosis agonist activities 'a 0.822 and 0.732, respectively). It is also noted that cinnamic :id is having better membrane integrity agonist activity (Pa .945) in comparison with curcumin (Pa 0.841) and isdesmethoxycurcumin (Pa 0.712). Cinnamic acid and sdesmethoxycurcumin (Pa 0.713 and 0.705, respectively), ın also be used for vascular (periferal) disease treatment. To ımmarize, the *in silico* analysis has indicated one or other ological properties for all the compounds included in the udy. The maximum (14) predicted activities were for curcumin followed by cinnamic acid (12), ascorbic acid (11) and camphor (10). The lowest number (3) of activities was predicted for niacin. However, the predicted activities varied from compound to compound. It is clear that approaches used in the present study help in probing biological function in greater depth. Such an approach, sometimes, may throw light on new properties hitherto unknown for the compound as reported elsewhere [17]. A blend of these compounds as in Ayurveda may be a better option for general treatment instead of formulations based on single molecules.

In conclusion, the *in silico* analysis of druggability and activity of the lead compounds in turmeric suggests that, in contrast to curcumin, other compounds also exhibited better druggability as well as activities. So, our approach identified some druggable leads from turmeric other than the popular curcumin. For specific disorders, drugs based on corresponding compounds can be developed to avoid any non-target effects. The structural alterations of leads are also possible by introducing combinatorial chemistry approach. So the current study motivates and initiates the screening of a diverse array of chemical compounds in other spices for their druggability. This approach may bring the success of phytochemicals in the treatment of many diseases and disorders with minimal side effects. Minimizing unwanted activities is as important as enhancing desired ones in reducing lead optimization cycle times and increasing the rate of entry of drug candidates into human testing [15].

High throughput pharmacological screening (HTPS) can be applied to crude plant extracts to overcome the slowness encountered in conventional methods [12, 15]. Evaluation of species and environmental libraries of whole plants has demonstrated the value of this approach for rapid prioritization of plants for investigation [12]. In future too, computational (*in silico*) methods are certain to play an increasingly important role in drug discovery [5]. If traditional concepts like Ayurveda are blended with modern concepts like above, the failure rates faced in today's drug discovery projects can be brought down.

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