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Exploration of new therapeutic potential of phytoconstituents in anti-inflammatory plants by PASS

Swati N. Hade

Department of Biotechnology, Sant Gadge Baba Amravati University, Amravati, Maharashtra, India

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ABSTRACT

Natural products have been the source of most of the active ingredients of today's medicines. Now a day this knowledge of ethnic use in medicines is being explored in much extent. At the end of 20th century, nearly half of the drugs approved are either were natural products or inspired by a natural compound. Despite these advantages, many large pharmaceutical companies have decreased the use of natural products in drug discovery screening due to the complexities present in natural compounds. Hence it becomes necessary to initially screen these natural compounds that exhibit multitargeted action. Therefore, biological activity has to be balanced with "drug-like" properties, and the closer we get to a candidate compound, the more important drug-likeness it becomes. So, PASS (Prediction of Activity Spectra for Substances) was employed as a feasible strategy so as to describe the biologically active properties of phytoconstituents. The present paper describes the application of online PASS for the evaluation of biological activity of main phytoconstituents in selected anti-inflammatory plants. Furthermore the unexplored but PASS predicted activities for particular phytoconstituents were described as hidden potential of these plants.

Keywords: Phytoconstituents, PASS, *Nelumbo*, *Polygonum*, *Aristolochia*.

INTRODUCTION

Drugs are of the most important concerns of human societies. Every year new drug generations are needed in order to cope with the new diseases and drug resistances. Among all diseases, cancer and inflammation are the most time consuming issues in the world of science and health [1].

Plant drugs have been the major source for treatment of diseases for a long time. They have been used in traditional medicine on the basis of experiences and practice. With the advent of modern systems of medicine need has been felt to investigate the active constituents present in these plants. Various herbal medicines that are popular among the public and improvements in their formulation have resulted in a new generation of phytomedicines that are more potent than before [2].

Natural product substances have historically served as the most significant source of new leads for pharmaceutical development. However, with the advent of bioinformatics, high throughput screening (HTS), molecular biology, biotechnology, combinatorial chemistry, in silico (molecular modeling) and other methodologies, the pharmaceutical industry has largely moved away from the plant derived natural products as a source for leads and prospective drug candidates [3].

The production cost of synthetic drugs is very high and also shows many side effects. It takes almost a decade to develop a new drug. On the other hand plant based drugs have long history of use and better patient tolerance as well as public acceptance. They are easily available at low cost as compare with modern drugs. Also phytoconstituents isolated from them may act as a lead compound for new pharmaceuticals [4].

In nature, natural compounds are specially adapted for their interactions with biological systems therefore, they are considered as valuable sources for drug discovery, but multitargeted actions of natural compounds could lead to additive/synergistic or antagonistic effects. Since there are several thousands of known pharmacological targets and natural products exhibit pleiotropic action interacting with multiple targets, therefore computer-aided methods could be extremely useful for natural products evaluation [5].

If the health of our society is to benefit from the diversity of compounds that have evolved in our flora, we need to maximize the chances of finding lead compounds and their active biological activities which could achieved by rational design of plant selection strategies, and cooperation between natural product chemists and those involved in drug development [6].

Generally, natural products research requires the utilization of virtual screening methods to find new lead substances. Currently, with development of sophisticated bioinformatics software's, such as PASS (*Prediction of Activity Spectra for Substances*) it has become feasible to explore the hidden pharmacological potential of selected traditional Indian medicinal plants based on their main phytoconstituents.

The biological activity spectra of these phytoconstituents obtained by PASS online (http://www.pharmaexpert.ru/PASSOnline/index.php) estimates the predicted activity spectrum of a compound as probable activity (Pa) and probable inactivity (Pi) [7]. Prediction of this spectrum by online PASS is based on their 2D structural formulae analysis containing more than 2,50,000 compounds exhibiting more than 3500 kinds of biological activities, including pharmacological effects, mechanisms of action, toxic and adverse effects, interaction with metabolic enzymes and transporters, its influence on gene expression etc.

The PASS prediction tool will predict the Pa: Pi (active: inactive ratio) at prediction threshold of Pa > 70%, 30% < Pa < 70%, Pa < 30%. If Pa > 0.7, the substance is very likely to exhibit the activity in experiment, but the chance of the substance being the analogue of a known pharmaceutical agent is also high. If 0.3 < Pa < 0.7, the substance is likely to exhibit the activity in experiment but the probability is less and the substance is unlike known pharmaceutical agents. If Pa < 0.3, the substance is unlikely to exhibit the activity in the experiment, however if the presence of this is confirmed in the experiment the substance might be a new entity [8].

This paper highlights on the use of online PASS as this is the only information available at an early stage for exploring the hidden pharmacological activities of some selected anti-inflammatory plants and its overview on their main phytoconstituents.

EXPERIMENTAL SECTION

In this study the genus *Nelumbo* from Nymphaceae, genus *Polygonum* from Polygonaceae and genus *Aristolochia* from Aristolochiaceae were selected (Table 1). These plants were considered as important source of anti-inflammatory drugs in the Asian subcontinent [9]. We have selected three main phytoconstituents of each genus based on their literature reports. The structure of these phytoconstituents were obtained from Pubchem and other reported literature. An extensive literature search was carried out to collect information about the common biological activities of these plants and their individual phytoconstituents (Supplement Table 1) using various search databases (PubMed, Sciverse, Web of knowledge and Google Scholar etc).

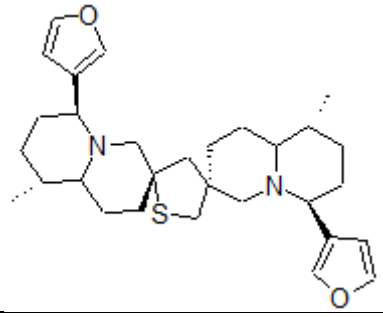
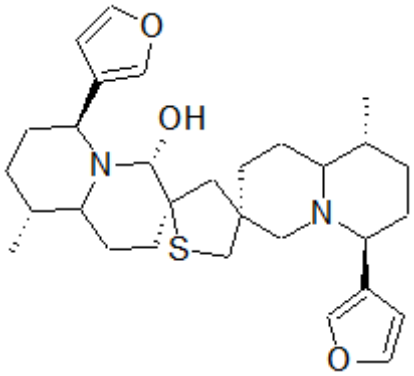
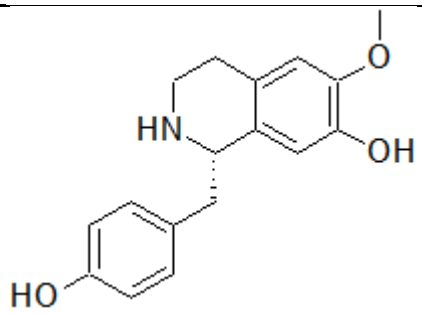
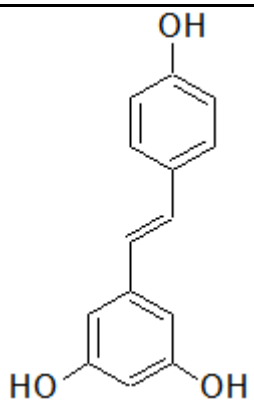
Activity of the molecule was predicted, using PASS (Prediction of Activity Spectra for Substances) which estimates the probable biological activity profiles for compounds under study based on their structural formulae presented in .MOLfile or .SDfile format using Marvin applet.

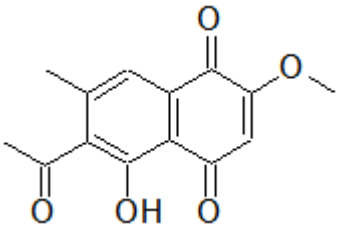
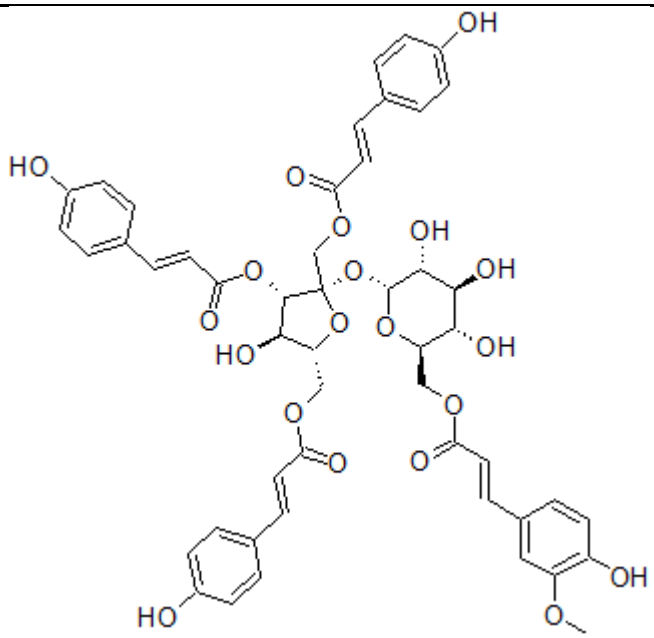
Molecule activity prediction is done by "comparing" the structure of query compound with the structure of well-known biological active substrate existing in database of the freely available PASS web service. Algorithm of activity spectrum estimation is based on Bayesian approach that estimates the probabilities of a molecule belonging to the classes of active and inactive compounds, respectively. Comparison of PASS prediction results with the experimental reported literature provides independent validation of the approach versus compounds in query with various kinds of biological activity. Average accuracy of prediction of online PASS is about 95% according to leave-one-out cross validation (LOO CV) estimation. Accuracy of PASS prediction depends on comprehensive information about biological activity spectrum for each compound available in PASS training set which is regularly updated therefore the estimate of biological activity tends to be more correct [10].

In this study, PASS prediction results (P_2) were analyzed and compared with the reported activities of plant (P_1), to obtain prediction coefficient (P) for each plant's three main phytoconstituent. Then the unpredicted but already

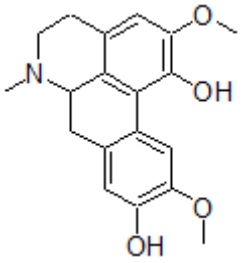
reported activities were matched with the PASS-predicted biological spectrum (P_3) of other known phytoconstituents in order to obtain the corrected prediction coefficient (P*) of the particular plant for further consideration of PASS applicability (Table 2; Supplement Table 1). Finally the unexplored but PASS predicted activities having score Pa > 0.5 for particular structure were listed as a hidden potential of the plant.

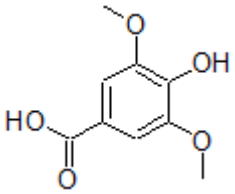
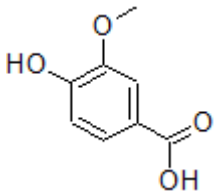
Table 1: Names of plants and their three main bioactive phytoconstituent selected for PASS prediction in this study (CID number refers to compound ID in Pubchem).

Sr. No.	Name of Phytoconstituent and their CID number	Structure of Phytoconstituent
Family: Nymphaeaceae **Genus:** *Nelumbo*		
1	Thiobinupharidine CID - 442554	
2	6 hydroxy thionuphlutine B CID - 10984042	
3	Coclaurine CID - 160487	
Family: Polygonaceae **Genus:** *Polygonum*		
4	Resveratrol CID - 445154	

5	Methoxystypandrone CID-158739	
6	Vanicoside B CID - 10033855	

Family: Aristolochiaceae **Genus:** *Aristolochia*

7	Isoboldine CID- 98369	

8	Syringic acid CID- 10742	
9	Vanllic acid CID- 8468	

RESULTS

1. Family : Nympheaceae
Genus: *Nelumbo*
Nelumbo is a genus of aquatic plants with large, showy flowers resembling water lilies, commonly known as Lotus. The generic name is derived from the Sinhalese word *Nelum*. The sacred lotus [*N. nucifera*] is native to Asia and this species is the national flower of Egypt, India and Vietnam [11]. It is commonly cultivated, and also used in cooking and Chinese traditional medicine as an antifebrile, sedative, and hemostat agent [12]. Previous phytochemical studies of the plant materials led to the isolation of some bisbenzylisoquinoline alkaloids [13] as well as benzylisoquinoline alkaloids [14, 15]. In recent years, bisbenzylisoquinoline alkaloids have received much attention because of their pharmacological effects such as antihypertensive activity, [15] anti-pulmonaryfibrosis [16] and anti-human immunodeficiency virus [HIV] activity [17, 18].

We have selected three main phytoconstituents, out of many alkaloids reported for this genus viz., Thiobinupharidine, 6-hydroxythionuphlutine B, Coclaurine as these are principal alkaloids and therefore used to predict the biological spectrum of this genus by PASS.

Table 2: PASS prediction coefficient based on the three main bioactive Phytoconstituent from each of three selected medicinally active herbs

Sr. No.	Plant Name *Genus*	Plant's main selected Phytoconstituent	P_1	P_2	P	P_3	P*
1	*Nelumbo*	Thiobinupharidine 6-hydroxy thionuphlutine B Coclaurine	17	8	0.47	7	0.88
2	*Polygonum*	Resveratrol Methoxystypandrone Vanicoside B	34	22	0.65	4	0.76
3	*Aristolochia*	Isoboldine Syringic acid Vanllic acid	18	8	0.44	6	0.78

Where, P_1, number of reported activities for the plant;
P_2, number of PASS predicted activities for the compound coincided with the reported activities;
P = P2/P1, prediction coefficient;
P_3, number of PASS predicted activities for the other phytoconstituents coincided with the reported activities;
P* = [P2+P3]/P1, corrected prediction coefficient

It was found that out of total 17 reported activities of the plant, 08 were predicted by PASS for these total 3 main phytoconstituents (prediction coefficient 0.47) (Table 2). The remaining reported activities of this genus which were not predicted by the PASS for these main phytoconstituents were correlated with the PASS predicted spectrum of the other reported phytoconstituents of this plant. It was found that out of remaining 10 activities, 07 were predicted by PASS for the other phytoconstituents present in the plant further correcting the prediction coefficient to 0.88 (Table 2, Supplement Table 2).

2. Family: Polygonaceae
Genus: *Polygonum*
Polygonum is a genus in the Polygonaceae family, commonly known as knotweed or knotgrass. The genus name is from the Greek *poly*, "many" and *gonu*, "knee" in reference to the swollen jointed stem. The genus primarily grows in northern temperate regions. They vary widely from prostrate herbaceous annual plants under 5 cm high, others erect herbaceous perennial plants growing to 3–4 m tall and yet others perennial woody vines growing to 20–30 m high in trees. Several are aquatic, growing as floating plants in ponds. The plant parts of *Polygonum* is used as a well-known traditional Chinese medicine (called Huzhang) officially listed in the Chinese Pharmacopoeia, and also used for folk medicine in Korea and Japan (called Japanese knotweed or bamboo). It is often used as an analgesic, antipyretic, diuretic, expectorant, and antitussive agent and also used for the treatment of chronic bronchitis, infectious hepatitis, diarrhea, cancer, hypertension, atherosclerosis, hyperlipidemia, leucorrhoea, dysmenorrhea, trauma with blood stasis, burn, snake bites, and allergic inflammatory diseases [19, 20, 21]. Plants belonging to this family are known to produce a large number of biologically important secondary metabolites, such as flavonoids, anthraquinones, alkaloids and steroids [22].

Polygonum sp. is interesting because they elaborate a series of stilbene derivatives including resveratrol, which has displayed so far a broad array of pharmacological effects [23]. Major bioactive compounds in *Polygonum* were identified as stilbenes (e.g., piceid, resveratroloside, and Resveratrol) and hydroxyanthraquinones (e.g., emodin, emodin-1-O-glucoside, and physcion). Both stilbenes and hydroxyanthraquinoines greatly contributed to the pharmalogical properties. We have selected three main phytoconstituents, out of many bioactive compounds reported for this genus viz., Resveratrol, Methoxystypandrone, Vanicoside B as these are principal compounds and therefore used to predict the biological spectrum of this genus by PASS.

It was found that out of total 34 reported activities of the plant 22 were predicted by PASS for these total 3 main phytoconstituents (prediction coefficient 0.65) (Table 2). The remaining reported activities of this genus which were not predicted by the PASS for these main phytoconstituents were correlated with the PASS predicted spectrum of the other reported phytoconstituents of this plant. It was found that out of remaining 12 activities 04 were predicted by PASS for the other phytoconstituents present in the plant further correcting the prediction coefficient to 0.76 (Table 2, Supplement Table 2).

3. Family: *Aristolochia*ceae
Genus: *Aristolochia*
Aristolochia is a genus of evergreen and deciduous woody vines and herbaceous perennials. Aristolochia contains many species from warm temperate to tropical regions throughout the world. Aristolochia comes from the Greek *aristos* meaning “best” or, originally, “most fitting” and *lochia* which mean "delivery.” This is due to its original use to expel the placenta after childbirth. The species mainly are climbing shrub [24]. *Aristolochia sp.* have been used in Brazilian traditional medicine as stomachic, antiophidian, antiinflammatory, antiasthmatic, and abortifacient agents [25], and more recently, in slimming therapy as a substitute for, or in addition to, medicinal plants [26]. Flavonols, dihydroflavonols, and isoflavonols have also been isolated from these species.

Aristolochia species have been shown to contain compounds belonging to these groups as well as other classes of alkaloids, such as aporphine [25], tetrahydroisoquinoline [25, 26], benzylisoquinoline and bisbenzylisoquinoline [27], 8-benzylberbine [28, 29], and 13-oxidodibenzo [a, g]-quinolizidinium [30]. We have selected three main phytoconstituents, out of many alkaloids reported for this genus viz., Isoboldine, Syringic acid, Vanllic acid as these are principal alkaloids and therefore selected as reference for the plant in PASS assessment.

It was found that out of total 18 reported activities of the plant 08 were predicted by PASS for these total 3 main phytoconstituents (prediction coefficient 0.44) (Table 2). The remaining reported activities of this genus which were not predicted by the PASS for these main phytoconstituents were correlated with the PASS predicted spectrum of the other reported phytoconstituents of this plant. It was found that out of remaining 10 activities 06 were predicted by PASS for the other phytoconstituents present in the plant further correcting the prediction coefficient to 0.78 (Table 2, Supplement Table 2).

Table 3: PASS predicted but not reported activities of selected phytoconstituents (Hidden potential of medicinal plants)

Sr. No.	Selected phytoconstituent	Sr. No.	Unexplored activities predicted by PASS	Pa	Pi
Genus: *Nelumbo*					
1	6- Hydroxythionuphlutine	1	Transcription factor inhibitor	0.794	0.035
		2	Phosphatase inhibitor	0.613	0.127
		3	Arrhythmogenic	0.541	0.113
2	Coclaurine	1	Spasmogenic	0.878	0.004
		2	Fibrinolytic	0.862	0.004
		3	Emetic	0.801	0.004
		4	Antidyskinetic	0.769	0.006
		5	Dopamine release stimulant	0.742	0.031
		6	Antiparkinsonian	0.720	0.01
		7	Transcription factor inhibitor	0.750	0.057
		8	Adrenergic	0.682	0.004
		9	Convulsant	0.688	0.056
		10	Myocardial ischemia treatment	0.690	0.088
3	Thiobinupharidine	1	Phosphatase inhibitor	0.653	0.109
		2	Cognition disorder treatment	0.557	0.031
		3	Cystic fibrosis treatment	0.457	0.046
		4	GABA A receptor antagonist	0.489	0.110
Genus: *Polygonum*					
4	Vanicoside B	1	Membrane integrity agonist	0.937	0.005
		2	Vasodilator, peripheral	0.721	0.016
		3	Sweetener	0.662	0.005
		4	Emetic	0.672	0.017
		5	Transcription factor inhibitor	0.722	0.074
5	Resveratrol	1	Membrane integrity agonist	0.925	0.008
		2	Mucomebranous protector	0.908	0.009
		3	Antiseborrheic	0.888	0.011
		4	Hypercholesterolemic	0.819	0.005
		5	Myocardial ischemia treatment	0.823	0.012
		6	Transcription factor inhibitor	0.83	0.022
		7	Peroxidase inhibitor	0.761	0.012
		8	Apoptosis agonist	0.748	0.017
		9	Ligase inhibitor	0.756	0.033
		10	Antihelminthic [Nematodes]	0.714	0.005
		11	Carminative	0.711	0.007
		12	Hematotoxic	0.760	0.063
		13	Antihypoxic	0.709	0.022
		14	Cytochrome P450 inhibitor	0.689	0.007
		15	Sickle-cell anemia treatment	0.715	0.04
		16	Neurotoxin	0.706	0.038
		17	Emetic	0.614	0.027
6	Methoxystypandrone	1	Membrane integrity agonist	0.903	0.014
		2	Kinase inhibitor	0.741	0.009
		3	Vascular [peripheral] disease treatment	0.696	0.021
		4	Antiseborrheic	0.726	0.083
		5	Myocardial ischemia treatment	0.670	0.109
		6	Mucomembranous protector	0.683	0.128
		7	Transcription factor inhibitor	0.651	0.124
		8	Emetic	0.527	0.043
Genus: *Aristolochia*					
7	Syringic acid	1	Superoxide dismutase inhibitor	0.890	0.006
		2	Shikimate 5-dehydrogenase inhibitor	0.868	0.001
		3	Hematotoxic	0.871	0.029
		4	Hypercholesterolemic	0.833	0.004
		5	Nitrate reductase[cytochrome inhibitor]	0.831	0.006
		6	NADH kinase inhibitor	0.819	0.007
		7	Fibrinolytic	0.813	0.005
		8	Transcription factor inhibitor	0.823	0.024
		9	Pulmonary hypertension treatment	0.808	0.013
		10	Urease inhibitor	0.753	0.005
		11	Myocardial ischemia treatment	0.762	0.032
		12	Antieborrheic	0.767	0.067
		13	Sickle-cell anemia treatment	0.728	0.036
8	Isoboldine	1	Spasmogenic	0.939	0.003
		2	Antiparkinsonian	0.895	0.004
		3	Emetic	0.876	0.002
		4	Antitussive	0.849	0.003

		5	Convulsant	0.787	0.026
		6	Dopamine release stimulant	0.746	0.03
		7	Transcription factor inhibitor	0.731	0.069
		8	Antineurotic	0.694	0.037
		9	Antihypoxic	0.647	0.046
		10	Myocardial ischemia treatment	0.633	0.152
9	Vanillic acid	1	Shikimate dehydrogenase inhibitor	0.910	0.001
		2	Fibrinolytic	0.882	0.004
		3	Methylenetetrahydrofolate reductase[NADPH] inhibitor	0.897	0.02
		4	Nitrate reductase[cytochrome] inhibitor	0.820	0.007
		5	Urease inhibitor	0.801	0.004
		6	Sickle-cell anaemia treatment	0.801	0.017
		7	Myocardial ischemia treatment	0.800	0.017
		8	Transcription factor inhibitor	0.802	0.032
		9	Dopamine release stimulant	0.774	0.023
		10	Antiseborrheic	0.776	0.063

DISCUSSION

The results of this study were able to justify the applicability of online PASS program for the prediction of three main phytoconstituent in the selected genus. It was found that some of the biological activities of plant reported from literature were not predicted by the online PASS. The complete information of available reports in the literature were not predicted by PASS as they consist of whole plant or plant extracts and the PASS predictions were based on the structure of the main phytoconstituent only. This may be the probable reason behind not complete PASS prediction as the plant extracts reported properties were due to the other phytoconstituents and in that they themselves shows varied biological activities. To include this justification we have included the reported activities of the PASS spectrum for the other phytoconstituents which have improved the average prediction coefficient to 0.81 for each genus. (Table 2, Supplement Table 2).

Generally natural products research requires the utilization of virtual screening methods to find new lead substances. But only a small part of structural diversity exhibited by plant compounds has been seriously explored for its pharmacological potential so far; and, therefore, new in-silico approaches are necessary to reveal novel biological activities of known natural products, including their interactions with the known biological targets and related pharmacotherapeutic effects [31]. While planning experiments and choosing the activities on which the compound has to be tested, it is necessary to be keep in mind the balance between the novelty of pharmacological action and the risk to obtain negative results in experimental testing. The computer aided drug designing like PASS will help to optimize the molecules and drug leads and will speed up the drug development process.

It was also found that there were a significant number of unexplored pharmacological activities obtained in the PASS spectrum of the selected phytoconstituent of the selected genus. As the PASS-predicted pharmacological activities with a score of Pa > 0.5 have a good chances to be obtained experimentally therefore only the unexplored pharmacological activities with a score of Pa > 0.5 have been summarized (Table 3).

All the nine phytoconstituents predicted by PASS shows a good tendency of having properties like transcription factor inhibitors and emetic. Transcription factor inhibitors are known to be important in cancer and inflammatory diseases and emetic is useful in emergency situations such as ingestion of toxin. Phytoconstituents from *Nelumbo* shows phosphatase inhibitor activity found in stress response signaling pathway and phytoconstituents from *Polygonum* shows membrane integrity agonist activity. These phytoconstituents also found to be play a major role in treatment of diseases like myocardial ischemia treatment and Parkinsons. Resveratrol found to be useful in treatment of sickle cell disease.

CONCLUSION

From these results, it can be concluded that PASS predictions of biological activity spectrum gives a fair approach for corresponding to the reported activities of phytoconstituents and determining the other valuable insights of other medicinal uses. However, PASS online is not be able to give an accurate prediction as they are based on 2D structure of the molecule and does not calculate the molecular energy levels. Hence, it is necessary for updating these properties so as to come up with a better valuable tool which will increase the prediction coefficient values.

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Exploration of new therapeutic potential of phytoconstituents in anti-inflammatory plants by PASS

SUPPLEMENTARY

Table 1: Reported activities of the selected plants (Ethno-medical, Pubmed, Sciverse reported)

Sr. No.	Reported Properties	Reference
	Nelumbo	
1	Antithrombic	1
2	Anti- HIV	2
3	Anti- Bleomycin induced	3
4	Antiinflamatory	4
5	Anticancer	5
6	Antipyretic	6
7	Antioxidant and Hepatoprotective	7
8	Antidiabetic	8
9	Antihepatoxic	10
10	Analgesic	10
11	Cholinsterase Activity	11
12	Antifertility	12
13	Antiobesity	13
14	Antiamnesic	14
15	Larvicidal and Insect repellant	15
16	Immunosuppressant	16, 82
17	Alzheimer	17
18	Antibacterial	18
	Polygonum	
19	Antioxidant	22
20	Antiinflamatory	24
21	Antitussive	25
22	Diuretic	35
23	Emmenagogue	26
24	Emollient	70
25	Febrifuge	71
26	Anticoagulant(Blood)	30
27	Anti ATPase	80
28	Cytoprotective IL-8 secretion Inhibitor	75
29	Antimicrobial	81
30	Estrogenic activity	72
31	SYK kinase Inhibitor	76
32	Lipid lowering effect	69
33	Immunostimulator	28
34	Anticancer	19
35	Antidiabetic	45
36	Antifungal	68
37	Anti-Osteoporosis	79
38	Rheumatoid Arthritis	74
39	Herbicide	77
40	Antileukemic	32
41	COX Inhibitor	33
42	Alzheimer	78
43	Analgesic	35
44	Antityrosinase activity	73
45	Anti-HIV	36, 42
46	Anti-Hepatic	37
47	Interferon inducing activity	38
48	Antiproliferative	40
49	Antinociceptive activity	39
50	Transmembrane permeability	41
51	Anti-Farnesyl protein transferase activity	43
52	Dermatologic	73
	Aristolochia	
52	Antiprotozoal	49
53	Antimycobacterial	49
54	Antiparasitic	49
55	Antidermatophytic	50
56	Insecticidal	52
57	Antivenom	54
58	Cytotoxic	55
59	Antibacterial	57, 83

60	Antineoplastic	60
61	Antinflamatory	61, 84
62	Antioxidant	61
63	Nephrotoxic	62
64	Antipyretic	62
65	Antitrypanosomal	63
66	Antiallergic	64
67	Interceptive and abortifacient activity	65
68	Antiimplantation and antioestrogenic activity	65, 67
69	Antiangiogenesis	66

Table 2: Reported Activities that were not predicted by PASS for the main phytoconstituent

Plant's name Genus	Plant's main selected Phytoconstituent	Sr. No.	Reported activities of plant, not predicted by PASS for the selected phytoconstituent of plant	Phytoconstituent responsible for the particular activity present in the plant (based on PASS)
Nelumbo	Thiobinupharidine	1	Antithrombic	Isoliensinine
		2	Anti- Bleomycin induced	Isolienisinine
		3	Antipyretic	N/P
	6-hydroxythionuphlutine B	4	Antidiabetic	Neferine
		5	Cholinesterase actvity	Cycloartenol
		6	Antifertility	N/P
	Coclaurine	7	Antiamnesic	Neferine
		8	Larvicidal and Insect repellent	Roemerine
		9	Immunosuppressant	(S)-armepavine
Polygonum	Resveratrol	1	Antitussive	N/P
		2	Diuretic	N/P
		3	Estrogenic activity	N/P
	Methoxystypandrone	4	Herbicide	N/P
		5	Analgesic	Quercetin
		6	Anti-Hepatic	Emodin
	Vanillic Acid	7	Antiproliferative	Lapathoside A
		8	Antimelanogenesis	Peceid
Aristolochia	Isoboldine	1	Antidermatophytic	N/P
		2	Insecticidal	Kusunokinin
		3	Antivenom	N/P
	Syringic acid	4	Cytotoxic	Cepharonone C
		5	Antibacterial	Aristolactam-N-β-D-glucopyanoside
		6	Antitrypanosomal	Copalic acid
	Vanillic acid	7	Interceptive and Abortifacient activity	Aristolochic acid
		8	Antimplantation and Antioestrogenic activity	Moupinamide

N/P – not predicted by PASS (the activity that is not contained in PASS list of activities)

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