Computer-Aided Discovery of Hidden Pharmacotherapeutic Potential in Phytoconstituents from Traditional Medicine

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Computer-Aided Discovery of Hidden Pharmacotherapeutic Potential in Phytoconstituents from Traditional Indian Medicine (TIM)

Supported by RFBR-DST grant No. 11-04-92713-IND_a/RUSP-1176
Meeting with Prof. Rajesh K. Goel at CRDRI (Feb. 2010)
Some Information About Natural Compounds

✓ At the end of XX century about 80 percent of the world population to some extend are using natural compounds as medicines\(^1\).

✓ Pharmaceuticals of vegetable or microbial origin make up more than 30% of global sales\(^2\).

✓ About 70% of NCEs were obtained on the basis of natural products in 1981-2006\(^3\).

\(^1\) World Health Organization
Advantages of Natural Compounds

✓ Greater chemical diversity in comparison with the compounds obtained using only synthetic methods.
✓ Better ADME/T characteristics.
Traditional Indian Medicine (Ayurveda)

- A lot of empirical knowledge about pharmacotherapeutic properties of natural products is accumulated in Traditional Indian Medicine (TIM) Ayurveda, which is known earlier than 1000 years BC.

- Some Ayurvedic plants are included into the list of national Indian priorities.
Problems with Study of Phytocomponents

✓ Utilization of extracts in a folk medicine.

✓ The difficulty of separation of each component in pure form.

✓ Changes in composition of components depending on the location and time of collection.

✓ Pleiotropic (multitargeted) action.
The empirical knowledge contained in Ayurveda can be currently analyzed using modern computer-aided methods. Such studies could give information about the basic mechanisms of TIM actions, providing the basis for rational design of new medicinal plant combinations, and identification of new lead compounds for future pharmaceuticals.
Requirements for a computer program evaluated biological activity profiles (spectra)

- Predicts (ideally) all known activities
- Possibility of training with new data
- Prediction on the basis of structural formulae (MOL or SDF)
- User-friendly interface
Biological activity is one of the most important characteristics of organic compound, which provides the basis for its use in therapeutic purposes. Biological activity reflects the result of interaction between the substance and biological object, and depends on substance structure and properties, biological object (species, sex, age), and mode of action (administration route, dose). **Biological activity spectrum of an organic compound is the set of different kinds of biological activity that reflect the results of the compound's interaction with various biological entities. It represents the "intrinsic" property of a substance depending only on its structure.** This is a qualitative characteristic property of a substance that depends only on its molecular structure.

Structure-activity relationships: (Q)SAR

Molecular descriptors
Sub-structural (-COO, -NH2, -OH, C6H5, и др.); physical-chemical (molecular weight, melting point, IR frequencies, chemical shifts in NMR, etc.); molecular connectivity, Wiener indices, Balaban indices, hydrophobicity constant, \( pK_a \), van der Waals volume, Log P, water solubility, etc. (several thousand).

Mathematical methods
Multiple linear regression (MLR); non-linear regression; partial least squares (PLS); regression on principal components (PCR); artificial neural networks (ANN); similarity matrices; genetic algorithms; support vector machine (SVM); cluster analysis (CA); discriminant analysis; etc.
The spatial configuration of the free uncharged molecules in the ground state in a vacuum is a necessary and sufficient description of its structure.

The use of this molecular structure description requires substantial computational resources for molecular modeling and/or quantum-chemical calculations.

However, the basis of all calculations is the traditional structural formula.

Thus, the structural formula uniquely determines all properties of the organic molecule.

Influence of the environment?

- Structural formula determines, at least, potential “intrinsic” properties of the molecule.
The most biological activities of organic compounds are the result of molecular recognition, which in turn depends on the correspondence between particular atoms of the ligand and the target.

\[
M = V + V_gM = V + V_gV + V_gV_gV + V_gV_gV_g + \ldots \\
M_i = V_i + V_i gM = V_i + V_i g(M_1 + M_2 + \ldots + M_m)
\]

Descriptors are based on the concept of atoms’ of molecule taking into account the influence of the neighborhoods:

**MNA** - **M**ultilevel **N**eighborhoods of **A**toms  
**QNA** - **Q**uantitative **N**eighborhoods of **A**toms  
**LMNA** - **L**abeled **M**ultilevel **N**eighborhoods of **A**toms

Substance representation: Clopidogrel

**Activity Spectrum**

- Abdominal pain
- Acute neurologic disorders treatment
- Agranulocytosis
- Allergic reaction
- Anaphylaxis
- Anemia
- Angioedema
- Angiogenesis inhibitor
- Antianginal
- Antiarthritic
- Anticoagulant
- Antineoplastic
- Antipsoriatic
- Antithrombotic

112 known activities in PASS SAR Base

**Structural formula**

**MNA Descriptors (1st and 2nd levels)**

<table>
<thead>
<tr>
<th>MNA Descriptor</th>
<th>Structural Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>C(C(CCC)C(CC-H-H)S(CC))</td>
</tr>
<tr>
<td>CHHHO</td>
<td>C(C(CCC)C(CS-H)-H(C))</td>
</tr>
<tr>
<td>CHHCC</td>
<td>C(C(CCC)N(CC-C)-H(C)-H(C))</td>
</tr>
<tr>
<td>CHHCCN</td>
<td>C(C(CCS)C(CC-H)C(CN-H-H))</td>
</tr>
<tr>
<td>CHCC</td>
<td>C(C(CCS)C(CN-H-H)-H(C)-H(C))</td>
</tr>
<tr>
<td>CHCCN</td>
<td>C(C(CC-H-H)N(CC-C)-H(C)-H(C))</td>
</tr>
<tr>
<td>CHCS</td>
<td>C(C(CC-H)C(CC-H)-H(C))</td>
</tr>
<tr>
<td>CCC</td>
<td>C(C(CC-H)C(CC-C)-H(C))</td>
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<tr>
<td>CCCS</td>
<td>C(C(CC-H)C(CC-C)-Cl(C))</td>
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<tr>
<td>CCCCl</td>
<td>C(C(CC-H)C(CC-Cl)-H(C))</td>
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<tr>
<td>CCOO</td>
<td>C(C(CC-H)C(CC-Cl)-C(CN-H-C))</td>
</tr>
<tr>
<td>NCCC</td>
<td>C(C(CC-H)S(CC)-H(C))</td>
</tr>
<tr>
<td>OC</td>
<td>N(C(C(CN-H-H)C(CN-H-H)-C(CN-H-C))</td>
</tr>
<tr>
<td>OCC</td>
<td>S(C(CCS)C(CS-H))</td>
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<tr>
<td>SCC</td>
<td>-H(C(CC-H))</td>
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<tr>
<td>CIC</td>
<td>-H(C(CC-H-H))</td>
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<td></td>
<td>-H(C(CN-H-H))</td>
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<tr>
<td></td>
<td>-H(C(CS-H))</td>
</tr>
<tr>
<td></td>
<td>-H(C(CN-H-C))</td>
</tr>
<tr>
<td></td>
<td>-H(H(-H-H-H-O))</td>
</tr>
<tr>
<td></td>
<td>-C(C(CC-C)N(CC-C)-H(-C)-C(-O-O))</td>
</tr>
<tr>
<td></td>
<td>-C(-H(-C)-H(-C)-H(-C)-O(-C-C))</td>
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<tr>
<td></td>
<td>-C(-C(CN-H-C)-O(-C)-O(-C-C))</td>
</tr>
<tr>
<td></td>
<td>-O(-C(-H-H-H-O)-C(-C-O-O))</td>
</tr>
<tr>
<td></td>
<td>-O(-C(-C-O-O))</td>
</tr>
<tr>
<td></td>
<td>-Cl(C(CC-Cl))</td>
</tr>
</tbody>
</table>
PASS: Prediction of Activity Spectra for Substances

Full text publications, databases, presentations at conferences etc.

Reliable data on structure and activity of drug-like molecules

PASS Training set
(~1 mln structures)

MNA descriptors

Training procedure

Bayesian algorithm

New molecule

SAR knowledgebase

Prediction results

PASS 2014 Characteristics

<table>
<thead>
<tr>
<th>Training Set</th>
<th>959,801 drugs, drug-candidates, pharmacological and toxic substances comprise the training set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Activity</td>
<td>7,158 biological activities can be predicted (Active vs. Inactive)</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Multilevel Neighborhoods of Atoms (MNA) descriptors [1, 2]</td>
</tr>
<tr>
<td>Mathematical Algorithm</td>
<td>Bayesian approach was selected by comparison of many different methods [2]</td>
</tr>
<tr>
<td>Validation</td>
<td>Average accuracy of prediction in LOO CV for the whole training set is ~95% [2]; robustness was shown using principal compounds from MDDR database [3]</td>
</tr>
</tbody>
</table>

Results of PASS Prediction for Clopidogrel

- **45 of 464 Possible Pharmacological Effects at Pa > Pi**
  - 0.951 0.004 Neuroprotector
  - 0.896 0.005 Acute neurologic disorders treatment
  - **0.723 0.006 Antithrombotic**
    - 0.712 0.004 Platelet aggregation inhibitor
    - 0.618 0.019 Antianginal
    - 0.553 0.013 Atherosclerosis treatment
    - 0.463 0.048 Analgesic
    - 0.385 0.009 Platelet antagonist
    - 0.361 0.027 Stroke treatment
    - 0.352 0.026 Angiogenesis stimulant
    - 0.332 0.017 Anticoagulant
    - 0.366 0.083 Diabetic neuropathy treatment
    - 0.292 0.013 Analgesic, opioid
    - 0.324 0.049 Antiinflammatory, ophthalmic
    - 0.341 0.116 Spasmolytic, urinary
    - 0.290 0.102 Cell adhesion molecule inhibitor
    - 0.301 0.135 Neurodegenerative diseases treatment
    - 0.261 0.098 Antipsoriatic
    - 0.167 0.005 Acetylcholine release stimulant
    - 0.199 0.057 Fibromyalgia syndrome treatment
    - 0.236 0.104 Age-related macular degeneration treatment
    - 0.202 0.075 Pancreatic disorders treatment
    - 0.228 0.104 Amyotrophic lateral sclerosis treatment
    - 0.375 0.254 Vasodilator, cerebral
    - 0.176 0.058 Lipoprotein disorders treatment
    - 0.156 0.047 Diabetic retinopathy treatment
    - 0.257 0.150 Psychotropic

- **42 Substructure Descriptors; 0 new.**
  - 246 of 6400 Possible Activities
  - 45 of 464 Possible Pharmacological Effects
  - 79 of 3850 Possible Mechanisms of Action
  - 106 of 321 Possible Toxic and Adverse Effects
  - 5 of 118 Possible Antitargets
  - 12 of 195 Possible Metabolism-Related Actions
  - 17 of 1610 Possible Gene Expression Regulation
  - 4 of 68 Possible Transporters-Related Actions
## Results of PASS Prediction for Clopidogrel

| Abdominal pain | Conjunctivitis | Henoch-Schönlein purpura | Purinergic P2 antagonist |
| Acute neurologic disorders | Consciousness alteration | Hepatic failure | Purinergic P2T antagonist |
| treatment | Constipation | Hepatitis | Purinergic P2Y antagonist |
| Agranulocytosis | Cough | Hepatotoxic | Purinergic P2Y12 antagonist |
| Allergic reaction | CYP2 substrate | Hypertensive | Purinergic receptor antagonist |
| Anaphylaxis | CYP2C substrate | Hyperthermic | Purpura |
| Anemia | CYP2C19 inhibitor | Hypotension | Renal colic |
| Angioedema | CYP2C19 substrate | Infection | Reproductive dysfunction |
| Angiogenesis inhibitor | CYP2C9 inhibitor | Insomnia | Rhinitis |
| Antianginal | CYP3A substrate | Lassitude | Sensory disturbance |
| Antiarthritic | CYP3A4 substrate | Leukopenia | Serum sickness |
| Anticoagulant | Cytochrome P450 inhibitor | Lichen planus | Shock |
| Antineoplastic | Dermatitis | Lichenoid eruption | Sinusitis |
| Antipsoriatic | Dermatologic | Malaise | Sleep disturbance |
| Antithrombotic | Dizziness | Menstruation disturbance | Stomatitis |
| Anxiety | Drug eruption | Myalgia | Syncope |
| Arthralgia | Dyspepsia | Nausea | THBS1 expression enhancer |
| Atherosclerosis treatment | Emetic | Necrosis | Thrombocytopenia |
| Back pain | Eosinophilia | Neuroprotector | Toxic |
| Behavioral disturbance | Erythema | Neutropenia | Toxic, gastrointestinal |
| Blindness | Erythema multiforme | Ocular toxicity | TP53 expression enhancer |
| Bronchoconstrictor | Exanthema | Pain | Urticaria |
| Cardiotoxic | Flatulence | Pancreatitis | Vasculitis |
| Cataract | GP IIb/IIIa receptor antagonist | Pancypetopenia | Vertigo |
| CCL4 expression enhancer | Hallucinogen | Platelet aggregation inhibitor | Vision disturbance |
| CCL5 expression enhancer | Headache | Platelet antagonist | |
| Chest pain | Heart failure | Pruritus | |
| Colic | Hematotoxic | Pulmonary embolism | |
| Colitis | Hemorrhage | | |

**Blue** – predictions coincided with the experiment.

**Black** – unpredictable activities.  **Red** – unpredicted activities.
PharmaExpert: Interpretation of the prediction results
Web-services based on our methods

Effective Solutions

Success Stories
Examples of use of our computational tools in drug discovery.

Personal Workspace
Storage and retrieval of structures and predictions, networking with the other participants of Way2Drug Community.

www.way2drug.com/Projects.php
Some examples of practical applications of biological activity spectra prediction

- Finding molecules with needed effects and MOA

- Athina Geronikaki, AUT, Greece
  - Search for multitarget drugs

- Marc Nicklaus, NCI/NIH, USA
  - Drug repurposing

- Rajesh Goel, PU, India
  - Estimating drug-drug interactions for phytoconstituents of medicinal plants

- Sergey Kryzhanovsky, Inst. of Pharmacol., Russia
Examples of search for new compounds based on predictions


PASS Biological Activity Spectrum Predictions in the Enhanced Open NCI Database Browser

Vladimir V. Poroikov,† Dmitrii A. Filimonov,† Wolf-Dietrich Ihlenfeldt,‡ Tatyana A. Gloriosoza,‡ Alexey A. Lagumin,¹ Yulina V. Borodina,† Alla V. Stepanchakova,‡ and Marc C. Nicklaus¶,*

Laboratory of Structure-Function Based Drug Design, V.N. Orekhovich Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, 10 Pogodinskaya Street, Moscow 109121, Russia, Computer Chemistry Center and Institute for Organic Chemistry, University of Erlangen-Nürnberg, Nächelsbächstrasse

Design of New Cognition Enhancers: From Computer Prediction to Synthesis and Biological Evaluation

Athina A. Geronikaki,§* John C. Dearden,† Dmitrii Filimonov,§ Irina Galaeva,§ Taisiya L. Garbobova,§ Tatiana Gloriosoza,‡ Valentina Krajneva,‡ Alexey Lagumin,§ Filiz Z. Macaev,‡ Guenadji Molodavin,‡ Vladimir V. Poroiko,§ Serghei I. Pogrebnoi,† Felix Shepeli,‡ Tatiana A. Voronina,§ Maria Tsitlakidou,‡ and Liudmila Vlad†

School of Pharmacy, Department of Pharmaceutical Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece

Computer-Aided Selection of Potential Antihypertensive Compounds with Dual Mechanism of Action

Alexey A. Lagumin,*, Paul Gomzikov, Dmitrii A. Filimonov, Tatyana A. Gureeva, Elvira A. Dlakyan, Elena V. Kugaevskaya, Yulina E. Elitsseeva, Nina I. Soloveyva, and Vladimir V. Poroikov

Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Pogodinskaya Street, Moscow 109121, Russia

Computer-Aided Discovery of Anti-Inflammatory Thiazolidinones with Dual Cyclooxygenase/ Lipoxigenase Inhibition

Athina A. Geronikaki,* Alexey A. Lagumin,† Dmitrii I. Hadjipavlov-Litina,§ Phacila T. Eleftheriou,† Dmitrii A. Filimonov,§ Vladimir V. Poroikov,§ Inshah Alani,§ and Anil K. Saxena§


Evaluation of the local anaesthetic activity of 3-aminobenzol[d]isothiazole derivatives using the rat sciatic nerve model

Athina Geronikaki*,§ Paola Vicini b, Nikos Babaracis c, Alexey Lagumin d, Vladimir Poroikov d, John Dearden e, Hassan Medaresi e, Mark Hewitt f, and George Theophilidis f

Multi-Targeted Natural Products Evaluation Based on Biological Activity Prediction with PASS

Alexey Lagumin, Dmitrii Filimonov and Vladimir Poroikov*

Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Pogodinskaya Street, Moscow 109121, Russia

Abstract: Natural products found a wide use in folk medicine. Presently, when routine development of new drugs faced a considerable challenge, they became an inspiration and valuable source in drugs discovery. Rather complex and diverse chemical structures of natural compounds provide a basis for calibration of different biological assays. Natural compounds exhibit a multiparametric action that may lead to additive, synergistic or antagonistic effects. Rational design of novel safe and potent pharmacocinetics requires an estimation of probable multiple actions of natural products. Our software PASS can perform such evaluation. It predicts with reasonable accuracy over 3000 pharmacokinetic effects, mechanisms of action, interaction with the metabolic system, and specific toxicity for drug-like molecules on the basis of these structural features. We analyzed PASS predictions utilizing Pharmascan, which performs selection of compounds with multiple mechanisms of action, analysis of active-active relationships and dose-dose interactions. The nature describes an
Sources of information about natural products:
Dictionary of Natural Products

Chemical, physical, and biological data on more than 259,859 compounds contained in over 68,000 entries.

http://dnp.chemnetbase.com/
Sources of information about natural products:
InterBioScreen Natural Compounds database

Over 55,000 natural compounds available in stock.
Natural products are used in folk medicine since many thousands year. They represent a significant, though often underappreciated resource for the development of new medicines.

Criteria:
1. Ayurvedic/traditional medicinal use;
2. Adequately explored for phytochemical analysis;
3. Unexplored for pleiotropic pharmacological studies.

Content:
1. 50 medicinal plants;
2. Structural formulae of 1906 phytochemicals;


http://way2drug.com/plants
Reference set of synthetic molecules: ChemBridge DVS
Comparison of three chemical libraries: distribution by molecular weights
Comparison of three chemical libraries: average number of biological activities*

*Predicted by PASS for one structure.
Comparison of three chemical libraries: pharmacological potential (PP)*

*PP = Number of predicted effects / Number of predicted mechanisms
Comparison of predicted and known activities for phytoconstituents from fifty TIM medicinal plants

Blue – predicted; red – not predicted

Exploited and Hidden Pharmacological Potential of Curcumin

Multi-targeted therapy by curcumin: how spicy is it?

Ajay Goel1, Sonia Jhurani2 and Bhart B. Aggarwal3

1Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA
2Cytochrome Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Although traditional medicines have been used for thousands of years, for most such medicines neither the active component nor their molecular targets have been very well identified. Curcumin, a yellow component of turmeric or curry powder, however, is an exception. Although inhibitors of cyclooxygenase-2, HER2, tumor necrosis factor, EGF-R, Bcr-abl, proteasome, and vascular endothelial cell growth factor have been approved for human use by the United States Food and Drug Administration (FDA), curcumin as a single agent can down-regulate all these targets. Curcumin can also activate apoptosis, down-regulate cell survival gene products, and up-regulate p53, p21, and p27. Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for treatment of most diseases, and it is inexpensive and has been found to be safe in human clinical trials. The present article reviews the key molecular mechanisms of curcumin action and compares this to some of the single-targeted therapies currently available for human cancer.

Keywords: Cancer / Curcumin / Cyclooxygenase / Multi-targeted therapy / Tumor necrosis factor

Received: September 7, 2007; revised: October 12, 2007; accepted: October 21, 2007
**In silico** mining several medicinal plants with desirable pleiotropic (anticonvulsant, antidepressant, and nootropic) effects

<table>
<thead>
<tr>
<th>No</th>
<th>Plant</th>
<th>Structure</th>
<th>Name</th>
<th>PASS predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Achyranthes aspera</em></td>
<td><img src="image1" alt="Structure" /></td>
<td>3-Pyrrolidine-carboxylic acid; N-Me</td>
<td>0.547 0.098 Nootropic</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>0.593 0.024 Anticonvulsant</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>0.281 0.069 Antidepressant</td>
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<tr>
<td>2</td>
<td><em>Aerva lanata</em></td>
<td><img src="image2" alt="Structure" /></td>
<td>6H-Indolo(3,2,1-de)(1,5)naphthyridin-6-one, 10-methoxy-</td>
<td>0.687 0.041 Nootropic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.285 0.138 Anticonvulsant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.205 0.111 Antidepressant</td>
</tr>
<tr>
<td>3</td>
<td><em>Berberis vulgaris</em></td>
<td><img src="image3" alt="Structure" /></td>
<td>Lambertine</td>
<td>0.386 0.231 Nootropic</td>
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<tr>
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<td></td>
<td></td>
<td>0.326 0.109 Anticonvulsant</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.469 0.026 Antidepressant</td>
</tr>
<tr>
<td>4</td>
<td><em>Glycyrrhiza glabra</em></td>
<td><img src="image4" alt="Structure" /></td>
<td>Cyclotetradecane</td>
<td>0.544 0.100 Nootropic</td>
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<td>0.406 0.067 Anticonvulsant</td>
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<td>0.218 0.102 Antidepressant</td>
</tr>
</tbody>
</table>

...
Predicted biological activities for major phytocomponents of Passiflora Incarnata: Harmine

0.674 0.045 Nootropic
0.698 0.004 5 Hydroxytryptamine 3A antagonist
0.557 0.081 Nerve growth factor agonist
0.469 0.031 Cyclic AMP phosphodiesterase inhibitor
0.499 0.091 Calcium channel (voltage-sensitive) activator
0.437 0.072 Cyclic AMP agonist
0.367 0.030 Calcium channel activator

0.116 0.336 Anticonvulsant
0.698 0.004 5 Hydroxytryptamine 3A antagonist
0.629 0.005 Cyclic AMP antagonist
0.438 0.038 Calmodulin antagonist
0.374 0.010 Benzodiazepine agonist partial

0.253 0.083 Antidepressant
0.745 0.023 5 Hydroxytryptamine release stimulant
0.698 0.004 5 Hydroxytryptamine 3A antagonist
0.557 0.081 Nerve growth factor agonist
0.414 0.046 5 Hydroxytryptamine 7 antagonist
0.351 0.039 Imidazoline receptor agonist
Predicted biological activities for major phytocomponents of Passiflora Incarnata: Harmaline

![Harmaline molecule](image)

- **0.704 0.036** Nootropic
  - 0.478 0.052 5 Hydroxytryptamine 3A antagonist
  - 0.443 0.039 Cyclic AMP phosphodiesterase inhibitor

- **0.269 0.150** Anticonvulsant
  - 0.478 0.052 5 Hydroxytryptamine 3A antagonist
  - 0.440 0.037 Calmodulin antagonist
  - 0.424 0.126 Cyclic AMP antagonist
  - 0.394 0.062 5 Hydroxytryptamine 7 antagonist

- **0.344 0.048** Antidepressant
  - 0.745 0.023 5 Hydroxytryptamine release stimulant
  - 0.478 0.052 5 Hydroxytryptamine 3A antagonist
  - 0.388 0.005 MAO inhibitor
  - 0.409 0.027 Imidazoline receptor agonist
  - 0.394 0.062 5 Hydroxytryptamine 7 antagonist
### Predicted biological activities for major phytocomponents of Passiflora Incarnata: Harmalol

<table>
<thead>
<tr>
<th>Activity</th>
<th>Probability</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nootropic</td>
<td>0.672</td>
<td>0.046</td>
</tr>
<tr>
<td>5 Hydroxytryptamine 3A antagonist</td>
<td>0.662</td>
<td>0.005</td>
</tr>
<tr>
<td>Calcium channel (voltage-sensitive) activator</td>
<td>0.568</td>
<td>0.044</td>
</tr>
<tr>
<td>Cyclic AMP phosphodiesterase inhibitor</td>
<td>0.409</td>
<td>0.050</td>
</tr>
<tr>
<td>Adrenaline release stimulant</td>
<td>0.330</td>
<td>0.034</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>0.245</td>
<td>0.170</td>
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<tr>
<td>5 Hydroxytryptamine 3 antagonist</td>
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<td>Cyclic AMP phosphodiesterase inhibitor</td>
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<tr>
<td>Cyclic AMP antagonist</td>
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<td>0.116</td>
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<td>Calmodulin antagonist</td>
<td>0.425</td>
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<tr>
<td>Antidepressant</td>
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<td>0.108</td>
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<td>5 Hydroxytryptamine 3 antagonist</td>
<td>0.662</td>
<td>0.005</td>
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<tr>
<td>MAO inhibitor</td>
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<tr>
<td>5 Hydroxytryptamine 7 antagonist</td>
<td>0.400</td>
<td>0.056</td>
</tr>
</tbody>
</table>
Revealing Medicinal Plants That Are Useful for the Comprehensive Management of Epilepsy and Associated Comorbidities through In Silico Mining of Their Phytochemical Diversity

Authors
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Key words
- Passiflora incarnata
- S. officinale
- epilepsy
- PASS
- PharmacoExpert
depression
- memory deficit

Abstract
In silico techniques in drug discovery may rationalise and speed up the identification of lead molecules from nature. Drug discovery from medicinal plants has mostly been confined to indications in accordance with their traditional use only. However, the availability of multiple phytoconstituents in medicinal plants suggests that these may be more useful beyond their traditional uses and in the management of chronic diseases, along with their comorbidities. In this study, the computer programmes PASS and PharmacoExpert were used to reveal the medicinal plants useful in the comprehensive management of epilepsy and associated psychiatric disorders based on the pleitropic effects predicted for their phytoconstituents. In silico analysis revealed that seven of 50 medicinal plants from traditional Indian medicine possessed the desired pleitropic effect, i.e., anticonvulsant, antidepressant, and nootropic activities. The majority of phytoconstituents from Passiflora incarnata were concurrently predicted to have the desired pleitropic effects. Therefore, P. incarnata was pharmacologically validated using the pentyleneetetrazole kindling mouse model. Behavioral and neurochemical evaluations confirmed the ameliorative role of P. incarnata in epilepsy and the associated depression and memory deficit. The pharmacological findings from this study propose that PASS and PharmacoExpert may serve as good tools for the optimisation of the selection of plants based on their phytoconstituents for the treatment of different ailments, even beyond their traditional use.

Abbreviations
- ACE: acetylcholinesterase
- AUC: area under the curve
- CPCSAN: Committee for the Purpose of Control and Supervision of Experiments on Animals
- DNP: Dictionary of Natural Products
- EPM: elevated plus maze
- FST: forced swim test
- LOOCV: leave-one-out cross-validation
- MNA: multilevel neighbourhods of atoms
- MOA: mechanisms of action
- NO: nitric oxide
- PA: probability "to be active"
- PASS: prediction activity spectra of substance
- PI: probability "to be inactive"
- PHE: Passiflora incarnata hydroethanolic extract
- PTZ: pentyleneetetrazole
- PHT: phenytoin
- SD: shock-free zone
- TST: tail suspension test

Supporting Information available online at http://www.thieme-connect.com

Introduction
Medicinal plants have been used for the treatment of various ailments in different systems of traditional medicine and have also served as a source for many drugs in modern medicine [1,2]. These plants have been explored either based on bioactivity-guided fractionation to identify bioactive principles for traditional activities of interest or based on the random exploration of the phytoconstituents without assigning any specific pharmacological activity [3,4]. In any case, these explorations have led to enrichment of the phytochemical information about these medicinal
Computer-aided discovery of biological activity spectra for anti-aging and anti-cancer olive oil oleoproteins

Predicted biological activity spectra for decarboxymethyl oleoprotein aglycone

Contribution of particular atoms to anti-aging/anti-cancer activities of OA and DOA

<table>
<thead>
<tr>
<th></th>
<th>OA</th>
<th>DOA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemiaceletic</td>
<td>Dialdehydic</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Pa = 0.672</td>
<td>Pa &lt; 0.2</td>
</tr>
<tr>
<td>Antinflammatory</td>
<td>Pa = 0.809</td>
<td>Pa &lt; 0.2</td>
</tr>
<tr>
<td>Antineoplastic</td>
<td>Pa = 0.510</td>
<td>Pa &lt; 0.2</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Pa = 0.419</td>
<td>Pa &lt; 0.2</td>
</tr>
</tbody>
</table>


- Positive impact: Green
- Neutral impact: Blue
- Negative impact: Red
Brahmi Ghrita: **Bacopa monnieri, Acorus calamus, Saussurea lappa and Evolvulus alsinoids**

All the plant extracts are blend with 84 % ghee

**Reported & predicted Pharmacological uses**

**PASS predicted novel Pharmacological uses**
More information could be found in our joint publications.
We have proposed the local correspondence concept, which is based on the fact that most biological activities of organic compounds are the result of molecular recognition, which in turn depends on the correspondence between the particular atoms of the ligand and the target.

Using this concept, we have developed a consistent system of atom-centered neighborhoods of atoms descriptors including MNA, QNA, and LMNA, and have implemented them in several SAR/QSAR/QSPR modeling approaches.
Components of Way2Drug platform (I)

PASS Online
Predicts about 4000 biological activity types of organic compounds by their structural formulas, including pharmacological effects, mechanisms of action, toxicity and side effects, interaction with metabolic enzymes, effects on gene expression, etc.

GUSAR Online
GUSAR online presents: consensus prediction, applicability domain assessment, internal and external models validation and clearly interpretations of obtaining results (acute rodents toxicity, antitargets, etc.).

DIGEP-Pred
Gene expression profiles are used to solve various problems in pharmaceutical research, such as the repositioning of drugs, overcoming resistance, estimating toxicity and drug-drug interactions.
Components of Way2Ddug platform (II)

**CLC-Pred**
Web-service for *in silico* prediction of cytotoxicity to the tumor and non-tumor cell-lines based on structural formula of chemical compound.

**META-Pred**
Prediction of interaction with 18 cytochrome P450 and UGT isoforms: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A10, UGT1A1, UGT2B7, UGT1A7, UGT2B15, UGT1A8, UGT1A4, UGT2B17, UGT2B10, UGT1A3, UGT1A9, UGT1A6, UGT2B4.

**SOMP**
Prediction of sites of metabolism for drug-like compounds for (five major human) cytochrome P450s: CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Also in the training set were included the sites of glucoronidation, catalyzed by UGT.
Way2Drug services are available online

12,949 users

91 country

- India
- Russia
- Ukraine
- Mexico
- China
- United States
- Egypt
- Kazakhstan
- Brazil
- Other
Over 300 papers published citing our web-services (>50% with the experimental confirmation; the other 50% - just with the prediction results without experiments)
### Somw publications with the experimental confirmation of prediction results for natural products

<table>
<thead>
<tr>
<th>№</th>
<th>Natural product</th>
<th>Activity</th>
<th>Experimental confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spirosolenol from roots of <em>Solanum anguivi</em></td>
<td>Antiinflammatory</td>
<td><em>in vitro</em></td>
</tr>
<tr>
<td>2</td>
<td>Phytocomponents of <em>Vitex negundo</em></td>
<td>Antioxidant, antineoplastic</td>
<td><em>in vitro</em></td>
</tr>
<tr>
<td>3</td>
<td>Phytocomponents of <em>Ficus religiosa L. (Moraceae)</em></td>
<td>Anticonvulsant GABA, Aminotransferase inhibitor</td>
<td><em>in vitro</em></td>
</tr>
<tr>
<td>4</td>
<td>Quercetin</td>
<td>Antiinflammatory, antibacterial</td>
<td><em>in vitro</em></td>
</tr>
<tr>
<td>5</td>
<td>Polyketides from marine-derived fungus <em>Ascochyta salicorniae</em></td>
<td>Protein phosphatase inhibitor</td>
<td><em>in vitro</em></td>
</tr>
</tbody>
</table>

There is dozen publications where the authors used our web-services for prediction of the biological activity spectrum of natural products with the experimental confirmation of the prediction results.

More info about the computational resources:

Chemo- and bioinformatics resources for *in silico* drug discovery from medicinal plants beyond their traditional use: a critical review

Alexey A. Lagunin, Rajesh K. Goel, Dinesh Y. Gawande, Priyanka Pahwa, Tatyana A. Gloriozova, Alexander V. Dmitriev, Sergey M. Ivanov, Anastasia V. Rudik, Varvara I. Konova, Pavel V. Pogodin, Dmitry S. Druzhilovsky and Vladimir V. Poroikov

*Teaser In silico approaches reveal mechanisms of adverse drug reactions and predict them at the earliest stages of drug development.*

*In silico* assessment of adverse drug reactions and associated mechanisms

Sergey M. Ivanov, Alexey A. Lagunin, and Vladimir V. Poroikov
General computer-aided approach to estimating the hidden pharmacotherapeutic potential of medicinal plants
## Comparison of predictions with known effects of *Aloe vera* phytocomponents

<table>
<thead>
<tr>
<th>No.</th>
<th>Known effects</th>
<th>Prediction by PASS and PharmExpert with the cutoff Pa &gt; 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Effects</td>
</tr>
<tr>
<td>1</td>
<td>Antibacterial</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Antifungal</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Anti-inflammatory</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Antimutagenic</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Antioxidant</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Antiprotozoal (Leishmania)</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Antiulcerative</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>Cardioprotectant</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>Cytostatic</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>Cytotoxic</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>Hepatoprotectant</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>Hypoglycemic</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Hypolipemic</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Immunostimulant</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>Neurodegenerative diseases treatment</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>Wound-healing agent</td>
<td>-</td>
</tr>
</tbody>
</table>

- **True Positives (TP)**: 11, 9, 12, 10, 14, 16
- **True Negatives (TN)**: 67, 63, 54, 67, 49, 28
- **False positives (FP)**: 39, 43, 52, 39, 57, 78
- **False negatives (FN)**: 5, 7, 4, 6, 2, 0

- **Sensitivity, TP/(TP+FN)**: 0.69, 0.56, 0.75, 0.63, 0.88, 1.00
- **Specificity, TN/(TN+FP)**: 0.63, 0.59, 0.51, 0.63, 0.46, 0.26
- **Precision, TP/(TP+FP)**: 0.22, 0.17, 0.19, 0.20, 0.20, 0.17
Natural products is a valuable source for creating novel medicines because they are particularly designed by “Mother Nature” for interaction with biological systems, and due to their great chemical and pharmacological diversity.

The hidden pharmacological potential of medicinal plants, their phytoconstituents and other natural products may be discovered using computer-aided analysis by PASS and PharmaExpert.

Way2Drug containing many computational predictive resources may become a platform for different collaborative projects in the field of drug discovery.
Acknowledgements to the key persons and to the financial support of our long-term efforts

Tatyana Gloriozova, M.Sc.
Alexey Lagunin, Dr. Sci.
Dmitry Filimonov, Ph.D.
Dmitry Druzhilovskiy, Ph.D.
Alexey Zakharov, Ph.D.

And to many other colleagues who participate(d) in our projects
Thank you for your kind attention!

Way2Drug
PREDICTIVE SERVICES
Understanding Chemical-Biological Interactions

We are open for collaboration.

Please, address your questions to:
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or
vvp1951@yandex.ru

www.way2drug.com