Computer-Aided Prediction of Biological Activity Spectra of Plant Based Cardiotonic Drugs

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Summary

The majority of biologically active compounds have both pharmacotherapeutic and side/toxic actions. To estimate general efficacy and safety of the molecules under study, their biological potential should be thoroughly evaluated. Based on a structural formulae of compounds presented as SDF or MOL-files, computer program PASS predicts the possible pharmacological effects, mechanism of action, and specific toxicity. An average accuracy of prediction in leave-one-out cross-validation is about 85%. The plant based cardiotonic drugs (Acetyldigoxin, Digitalin, Digitoxin, Digoxin and Ouabain**)** selected for this study is pharmacologically screened by the computational programme PASS for its complete activity spectrum analysis. The drugs show anti-diarrheal, arrhythmogenic, cardiotonic and cardiotoxic activity in-silico.

Key word: Cardiotonic drugs, Digitalis, PASS, Biological activity,

Introduction

Cardiotonics are medications that increase the strength of muscle contractions that pump blood from and out of the heart. The main medical treatment for heart failure is given by the inotropic drug digoxin . A drug derived which has been used to treat heart disease for more than 300 years derived form the foxglove plant, makes the heart contractions stronger, reduce heart size, lessen the frequency or severity of some heart arrhythmias. When atherosclerosis are worse, as an immediation it dialates the blood vessel and assure the flow of blood in and out of the heart.

Computer-assisted structure-activity studies are a powerful tool for the elucidation of the relationship between the molecular structure of a chemical and its biological activity. Structure-activity relationships could aid in the first phase screening of chemotherapeutic agents or hazardous substances for testing in vivo and in vitro. Many work has been published in this field of research, structure-activity studies with computer assistance have been performed successfully to predict the carcinogenic activity of N -nitrosamines, aromatic amines, polycyclic aromatic hydrocarbons, and the antineoplastic activity of aniloacridines [(1-6).]

Digoxin is an example of a cardio-active or cardiotonic drug, a steroid which exerts powerful action on the contraction of cardiac muscle in animals. It has been used in the treatment of heart conditions since its discovery in 1775[9]. *Digitalis* is a genus of about 20 species of herbaceous perennials, shrubs, and biennials that are commonly called foxgloves. It belongs to the Plantaginaceae [8] **.** The scientific name means "finger-like" and refers to the ease with which a flower of *Digitalis purpurea* can be fitted over a human fingertip. The best-known species is the Common Foxglove *(Digitalis purpurea).* A group of pharmacologically active compounds are extracted mostly from the leaves of the second year's growth, and in pure form are referred by common chemical names such as ***digitoxin*** or ***digoxin***, or by brand names such as *Crystodigin* and *Lanoxin*, respectively. The two drugs differ in an additional hydroxyl group at the C-3 position on the B-ring (adjacent to the pentane). Both molecules include a lactone and a triple-repeating sugar called a glycoside. The crude preparations containing cardiac glycosides, particularly digoxin, are colloquially called as digitalis. Digitalis has not been shown to improve survival of heart patients, but it does relieve symptoms and may reduce hospitalizations. Many experts now prescribe drugs proven to prolong life, such as an ACE inhibitor or beta-blocker before digitalis is tried. Digitalis may be useful, however, especially if used in combination with other agents for patients with:

- Systolic dysfunction characterized by a low ejection fraction, or EF (the percentage, or fraction, of blood pumped out of the heart with each beat)
- Heart failure and atrial fibrillation, a rapid, irregular heartbeat arising in the upper chamber. Digoxin (Lanoxin) is the most commonly prescribed form of digitalis [10].

In our present study we have derived a set of actions that this drug could drive in our body. It is done through the computational prediction of structure activity relationship. Further studies are initiated to thrive excellence in this field of synthesizing a great cardiovascular drug combination.

Materials and Methods

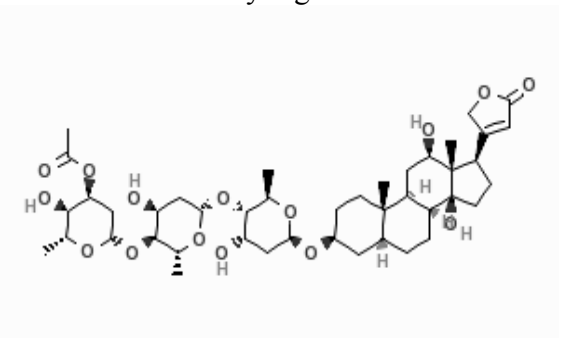
The structures of the Cardiotonic drugs [7] (Acetyldigoxin, Digitalin, Digitoxin, Digoxin and Ouabain) are obtained from the pubchem compound repository in SDF format. The biological activity spectrum was drawn using the activity prediction server PASS – Prediction of Activity Spectra of Substances.

Cardiotonic drugs selected for this study

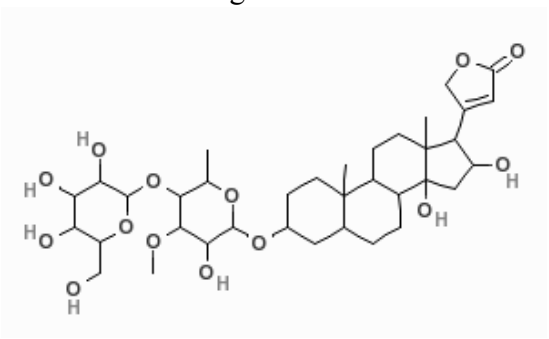
Cardiotonic Drugs	Plant Source	Common Name
Acetyldigoxin	*Digitalis lanata*	Grecian foxglove, woolly foxglove
Digitalin	*Digitalis purpurea*	Purple foxglove
Digitoxin	*Digitalis purpurea*	Purple foxglove
Digoxin	*Digitalis purpurea*	Purple or common foxglove
Ouabain	*Strophanthus gratus*	Ouabain tree

CHEMICAL STRUCTURES OF CARDIOTONIC DRUGS

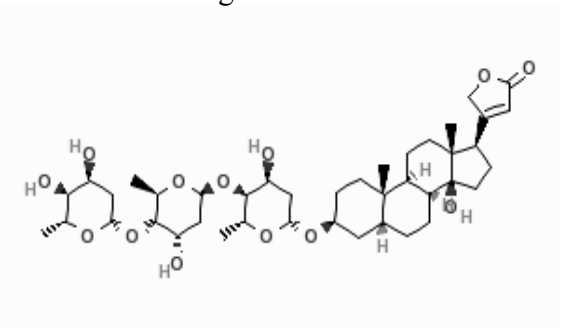
Acetyldigoxin



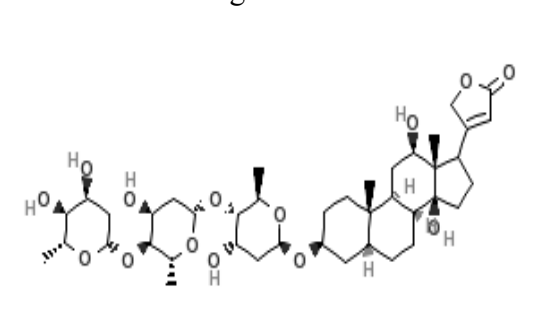
Digitalin



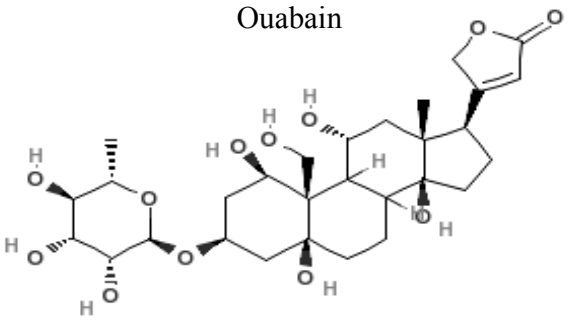
Digitoxin



Digoxin



Ouabain



Multilevel Neighborhoods of Atoms (MNA) structure descriptors of a molecule are generated on the basis of connection between the compounds present in the structure. The data on the activity prediction is based on the physical position, stacking configuration and intercalations of molecule. Bond types are not specified (topological approximation) at many instances and its strength in a molecule adds an effect on the activity. All hydrogen based on valences and partial charges of atoms are taken into account. The structure of a molecule is represented as the set of multilevel neighborhoods of atom's descriptors calculated iteratively. Zero-level's descriptor is presented by the type of atom and special dash label if the atom is not included into the cycle. This process is extended from the 1st level to the 2nd, 3rd, etc. neighborhoods of the atom.

Biological activity is the result of a chemical compound's interaction with a biological entity. In clinical trial, a biological entity is represented by a human organism. In preclinical testing, it is the experimental in animals (in vivo) and other experimental models (in vitro). Biological activity depends on the peculiarities of a compound (structure and physico-chemical properties), biological entity (species, sex, age, etc.), mode of treatment (dose, route, etc.) in silico.

Results and Discussion

The activities of the respective compounds are given below in the tabular column.

Acetyldigoxin

70 Substructure descriptors; 0 new.
10 Possible activities at Pa > 70%
Pa Pi for Activity:

0,926	0,006	Cardiotonic
0,865	0,007	Cardiotoxic
0,851	0,005	Emetic
0,788	0,006	CYP3A2 substrate
0,782	0,017	Cholesterol synthesis inhibitor
0,772	0,009	Ecdysone 20-monooxygenase inhibitor
0,712	0,012	Antidiarrheal
0,721	0,031	Arrhythmogenic
0,702	0,013	Nerve growth factor agonist
0,735	0,063	Hematotoxic

Digitalin

67 Substructure descriptors; 0 new.
8 Possible activities at Pa > 70%
Pa Pi for Activity:

0,951	0,005	Cardiotonic
0,900	0,006	Cardiotoxic
0,890	0,003	Emetic
0,822	0,042	Hematotoxic
0,783	0,015	Arrhythmogenic
0,773	0,015	Licheninase inhibitor
0,738	0,001	Na+ K+ transporting ATPase inhibitor
0,739	0,008	Antidiarrheal

Digitoxin

56 Substructure descriptors; 0 new.
Antiarrhythmic
Cardiotonic
Diuretic
Spasmogenic
10 Possible activities at Pa > 70%
Pa Pi for Activity:

0,974	0,005	Cardiotonic
0,949	0,005	Cardiotoxic
0,899	0,003	Emetic
0,885	0,027	Hematotoxic
0,828	0,005	CYP3A2 substrate
0,812	0,010	Arrhythmogenic
0,801	0,001	Na+ K+ transporting ATPase inhibitor
0,801	0,006	Antidiarrheal
0,783	0,017	Cholesterol synthesis inhibitor
0,748	0,013	GABA A receptor antagonist

Digoxin

57 Substructure descriptors; 0 new.
Teratogen
Antiarrhythmic
Cardiotonic
Diuretic
CYP3A substrate
CYP3A2 substrate
Na+ K+ transporting ATPase inhibitor
12 Possible activities at Pa > 70%
Pa Pi for Activity:

0,970	0,005	Cardiotonic
0,928	0,006	Cardiotoxic
0,886	0,004	Emetic
0,874	0,030	Hematotoxic
0,796	0,007	Ecdysone 20-monooxygenase inhibitor
0,790	0,014	Arrhythmogenic
0,768	0,006	CYP3A2 substrate

0,763	0,007	Antidiarrheal
0,773	0,019	Cholesterol synthesis inhibitor
0,749	0,001	Na+ K+ transporting ATPase inhibitor
0,742	0,014	GABA A receptor antagonist
0,701	0,019	Glyceryl-ether monooxygenase inhibitor

Ouabain

61 Substructure descriptors; 0 new.

Toxic

Cardiotonic

Emetic

Adenylate cyclase inhibitor

Cardiotoxic

4-Nitrophenylphosphatase inhibitor

8 Possible activities at Pa > 70%

Pa Pi for Activity:

0,954	0,005	Cardiotonic
0,895	0,006	Cardiotoxic
0,828	0,005	Emetic
0,821	0,009	Arrhythmogenic
0,738	0,008	Antidiarrheal
0,725	0,007	CYP3A2 substrate
0,768	0,054	Hematotoxic
0,726	0,024	Licheninase inhibitor

Pa and Pi are the estimates of probability for the compound to be active and inactive respectively for each type of activity from the biological activity spectrum. Their values vary from 0.000 to 1.000. Usual interpretation of prediction results is based on the Pa values. If Pa > 0.7 the chance to find the activity in experiment is high, but in many cases the compound may occur to be the close analogue of known pharmaceutical agents. If 0.5 < Pa < 0.7 the chance to find the activity in experiment is less, but the compound is not so similar to known pharmaceutical agents. If Pa < 0.5 the chance to find the activity in experiment is even more less, but if it will be confirmed the compound might occur to be a New Chemical Entity.

Digitalis works by inhibiting sodium-potassium ATPase, the result is an increased intracellular concentration of sodium, which in turn increases intracellular calcium by passively decreasing the action of the sodium-calcium exchanger in the sarcolemma. The increased intracellular calcium gives a positive inotropic effect. It also has a vagal effect on the parasympathetic nervous system, and as such is used in reentrant cardiac arrhythmias and to slow

the ventricular rate during atrial fibrillation. The dependence on the vagal effect means that digitalis is not effective when a patient has a high sympathetic nervous system drive, which is the case with acutely ill persons, and also during exercise.

Conclusion

The results show that the compounds are well enough to be a cardiotonic but on over dosage it may be cardiotoxic. The drug also shows emetic sensation on administration. They also act as antidiarrheal and arrhythmogenic . This shows that in future it may be designed as a drug for the control of diarrhea. Further studies on this prediction have to be done in order to get the full results on its activity spectrum.

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