

DIGITALIS THERAPY IN PATIENTS WITH CONGESTIVE HEART FAILURE

Dr. B. Anil Reddy

Maheshwara College of Pharmacy, Department of Pharmaceutical sciences, Hyderabad, Andhra Pradesh.

Email: drbanilreddy@gmail.com

ABSTRACT

Herbal Medicine, sometimes referred to as Herbalism or Botanical Medicine, is the use of herbs for their therapeutic or medicinal value. An herb is a plant or plant part valued for its medicinal, aromatic or savory qualities. Herb plants produce and contain a variety of chemical substances that act upon the body. The term digitalis or digitalis compounds are all used to refer to the entire group of inotropic (or drugs that increase myocardial contractility). All glycosides have a shared structure of: an aglycone ring structure. The aglycone ring is where the pharmacological activity is found. The main use of Digitalis Purpurea today is as a effective way of treating congestive heart failure. As a group they are classified as cardiac inotropes. Cardiac, of course, refers to the heart. An inotrope is a substance that has a direct effect on muscle contraction. Positive inotropism is an increase in the speed and strength of muscle contraction, while negative inotropism is the opposite. Digitalis has a positive inotropic effect on the heart muscle. During the early 20th century, the drug was introduced as treatment of atrial fibrillation. Only subsequently was the value of digitalis for the treatment of congestive heart failure (CHF) established.

Keywords: Digitalis, Congestive heart failure, Therapy.

INTRODUCTION

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history. It was an integral part of the development of modern civilization. Primitive man observed and appreciated the great diversity of plants available to him. The plants provided food, clothing, shelter, and medicine. Much of the medicinal use of plants seems to have been developed through observations of wild animals, and by trial and error. As time went on, each tribe added the medicinal power of herbs in their area to its knowledgebase¹. They methodically collected information on herbs and developed well-defined herbal pharmacopoeias. Indeed, well into the 20th century much of the pharmacopoeia of scientific medicine was derived from the herbal lore of native peoples. Many drugs commonly used today are of herbal origin. The physician/scientist credited with bringing digitalis into mainstream medicine is William Withering. Foxglove¹⁰ had already been in use as a traditional herbal remedy¹¹ for "dropsy," the swelling that often accompanies heart failure. In the 1780s, Withering observed the remarkable effectiveness of digitalis/foxglove in a woman who had dropsy, and he began a rigorous study of the drug. Digitalis is a drug that has been used for centuries to treat heart disease. The active ingredient in the drug is glycoside, a chemical compound that contains a sugar molecule linked to another molecule. The glycoside compound can be broken down into a sugar and nonsugar compound. Though current digitalis drugs are synthetic, that is, man-made, early forms of the drug were derived from a plant. Digitalis is a derivative of the plant *Digitalis purpurea*, or purple foxglove. The plant's name, *Digitalis* (from the Latin digit, finger) describes the finger-shaped purple flowers it bears. The effects of the plant extract⁹ on the heart were first observed in the late eighteenth century by William Withering, who experimented with the extract in fowls and humans. Withering reported his results in a

treatise entitled, "The Foxglove and an Account of its Medical Properties, with Practical Remarks on Dropsy." His explanations of the effects of foxglove on the heart have not stood up to the test of time, but his prediction that it could be "converted to salutary ends" certainly has. Indeed, digitalis remains the oldest drug in use for the treatment of heart disease, as well as the most widespread, in use today.

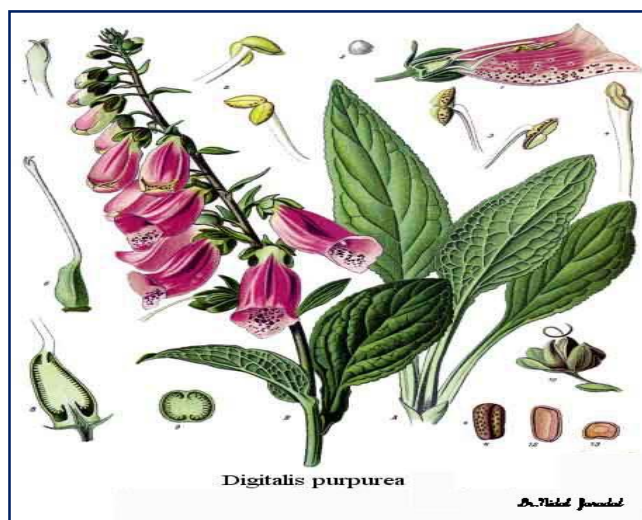
BIOLOGICAL SOURCES

*Digitalis*² is a biennial or perennial herb that grows up to about 1.2 meters height. The lower basal leaves of the plant are long stalked, hairy and egg shaped and the upper leaves are almost without stalks, becoming smaller in size as they go upwards. It has white or purple flowers and egg shaped fruits.

Botanical Name: *Digitalis purpurea* (Linn.)

Family: N.O. Scrophulariaceae

Indian Name: Tilpushpi



CONSTITUENTS

Digitalis contains four important glucosides of which three are cardiac stimulants. The most powerful is Digitoxin, an extremely poisonous and cumulative drug, insoluble in water, Digitalin, which is crystalline and also insoluble in water; Digitalein, amorphous, but readily soluble in water, rendering it, therefore, capable of being administered subcutaneously, in doses so minute as rarely to exceed of a grain; Digitonin, which is a cardiac depressant, containing none of the physiological action peculiar to Digitalis, and is identical with Saponin, the chief constituent of Senega root. Other constituents are volatile oil, fatty matter, starch, gum, sugar, etc. The amount and character of the active constituents vary according to season and soil: 100 parts of dried leaves yield about 1.25 of Digitalin, which is generally found in a larger proportion in the wild than in the cultivated plants. The active constituents of Digitalis are not yet sufficiently explored to render a chemical assay effective in standardizing for therapeutic activity. The different glucosides contained varying from each other in their physiological action, it is impossible to assay the leaves by determining one only of these, such as Digitoxin. No method of determining Digitalin is known. Hence the chemical means of assay fail, and the drug is usually standardized by a physiological test. One of our oldest firms of manufacturing druggists standardizes preparations of this extremely powerful and important drug by testing their action upon frogs.

PREPARATIONS

The preparations of Foxglove on the market vary considerably in composition and strength. Powdered Digitalis leaf is administered in pill form. The pharmacopoeial tincture, which is the preparation in commonest use, is given in doses of 5.15 minims, and the infusion is the unusually small dose of 2 to 4 drachms, the dose of other infusions being an ounce or more. The tincture contains a fair proportion of both Digitalin and Digitoxin.

CULTIVATION

The Foxglove is cultivated by a few growers in this country in order to provide a drug of uniform activity from a true type of *Digitalis purpurea*. It is absolutely necessary to have the true medicinal seeds to supply the drug market: crops must be obtained from carefully selected wild seed and all variations from the new type struck out. The plant will flourish best in well drained loose soil, preferably of siliceous origin, with some slight shade. The plants growing in sunny situations possess the active qualities of the herb in a much greater degree than those shaded by trees, and it has been proved that those grown on a hot, sunny bank, protected by a wood, give the best results. It grows best when allowed to seed itself, but if it is desired to raise it by sown seed, 2 lb. of seed to the acre are required. As the seeds are so small and light, they should be mixed with fine sand in order to ensure even distribution. They should be thinly covered with soil. The seeds are uncertain in germination, but the seedlings may be readily and safely transplanted in damp weather, and should be pricked out to 6 to 9 inches apart. Sown in spring, the plant will not blossom till the following year.

Seeds must be gathered as soon as ripe. The flowers of the true medicinal type must be pure, dull pink or magenta, not pale-coloured, white or spotted externally. It is estimated that one acre of good soil will grow at least two tons of the Foxglove foliage, producing about 1/2 ton of the dried leaves.

MEDICINAL ACTION AND USES

Digitalis has been used from early times in heart cases. It increases the activity of all forms of muscle tissue, but more especially that of the heart and arterioles, the all-important property of the drug being its action on the circulation. The first consequence of its absorption is a contraction of the heart and arteries, causing a very high rise in the blood pressure³. After the taking of a moderate dose, the pulse is markedly slowed. Digitalis also causes an irregular pulse to become regular. Added to the greater force of cardiac contraction is a permanent tonic contraction of the organ, so that its internal capacity is reduced, which is a beneficial effect in cases of cardiac dilatation, and it improves the nutrition of the heart by increasing the amount of blood. In ordinary conditions it takes about twelve hours or more before its effects on the heart muscle is appreciated, and it must thus always be combined with other remedies to tide the patient over this period and never prescribed in large doses at first, as some patients are unable to take it, the drug being apt to cause considerable digestive disturbances, varying in different cases. This action is probably due to the Digitonin, an undesirable constituent. The action of the drug on the kidneys is of importance only second to its action on the circulation. In small or moderate doses, it is a powerful diuretic and a valuable remedy in dropsy, especially when this is connected with affections of the heart. It has also been employed in the treatment of internal haemorrhage, in inflammatory diseases, in delirium tremens, in epilepsy, in acute mania and various other diseases, with real or supposed benefits. The action of Digitalis in all the forms in which it is administered should be carefully watched, and when given over a prolonged period it should be employed with caution, as it is liable to accumulate in the system and to manifest its presence all at once by its poisonous action, indicated by the pulse becoming irregular, the blood-pressure low and gastro-intestinal irritation setting in. The constant use of Digitalis, also, by increasing the activity of the heart, leads to hypertrophy of that organ. Digitalis is an excellent antidote in Aconite poisoning, given as a hypodermic injection. When Digitalis fails to act on the heart as desired, Lily-of-the-Valley may be substituted and will often be found of service. In large doses, the action of Digitalis on the circulation will cause various cerebral symptoms, such as seeing all objects blue, and various other disturbances of the special senses. In cases of poisoning by Digitalis, with a very slow and irregular pulse, the administration of Atropine is generally all that is necessary. In the more severe cases, with the very rapid heartbeat, the stomach pump must be used, and drugs may be used which depress and diminish the irritability of the heart, such as chloral and chloroform.

HEALTH BENEFITS OF DIGITALIS

Digitalis is of value in irritable heart with palpitation from overwork, heart strain, and the arrhythmia of simple dilatation, in moderate degrees of ventricular dilatation, and cardiac asthenia. It is especially commended for the irritable heart of soldiers brought on by long marches and fighting whereby the inhibitory-control is lost or lessened and exhaustion of the heart-muscle is imminent. When palpitation is purely nervous, it is of little value; cactus is then a better remedy. It also fails often in paroxysmal tachycardia, which is also mostly a nervous phenomenon. In Grave's disease, it is not curative, but sometimes rectifies the cardiac irregularity. In functional palpitation arising from imperfect digestion it sometimes controls the heart symptoms, but gives little or no relief if the trouble is purely nervous, nor does it aid the stomachic disorder. Digitalis is a classic example of a drug derived from a plant formerly used by folklorists and herbalists: herbalists have largely abandoned its use because of its narrow therapeutic index and the difficulty of determining the amount of active drug in herbal preparations. Once the usefulness of digitalis in regulating pulse was understood, it was employed for a variety of purposes, including the treatment of epilepsy and other seizure disorders, now considered inappropriate. Below are some of the medicinal properties of digitalis: Digitalis is mainly used in treating heart diseases. In case of congested heart failure, it promotes and stimulates the activity of all muscle tissues. The herb forces more blood into the coronaries thereby improving the nourishment to the heart. When blood circulation gets impaired and dropsy sets in, digitalis help in restoration and regulation of the function of the heart. It helps urination by improving the blood supply to the kidneys and removes obstructions within the kidneys. Digitalis is used with gratifying results in some ointment for local application on wounds and burns. In cases of burns, it is very effective in preserving severely damaged cells.

CHEMISTRY

Ornamental strains of *D. purpurea* typically have low concentrations of active compounds. Leaves of wild varieties that have been used for medicinal purposes contain at least 30 different glycosides in total quantities ranging from 0.1% to 0.6%; these consist primarily of purpurea glycoside A (yielding digitoxin) and glycoside B, the precursor of gitoxin. Upon hydrolysis, digitoxin and gitoxin lose sugar molecules, producing their respective aglycones, digitoxigenin, and gitoxigenin. Seeds also contain digitalis glycosides. The main glycosides of *D. lanata* are the lanatosides, designated A through E. Removal of acetate groups and sugars results in formation of digitoxin, gitoxin, digoxin, digitalin, and gitaloxin. *D. lanata* is not typically used in powder form in the United States, but serves as a major source of lanatoside C and digoxin.

PATHOPHYSIOLOGY

Digoxin's inotropic effect results from the inhibition of the sodium-potassium adenosine triphosphatase ($\text{Na}^+/\text{K}^+\text{ATPase}$) pump. The subsequent rise in intracellular calcium (Ca^{++}) and sodium (Na^+) coupled

with the loss of intracellular potassium (K^+) increases the force of myocardial muscle contraction (contractility), resulting in a net positive inotropic effect. Digoxin also increases the automaticity of Purkinje fibers but slows conduction through the atrioventricular (AV) node. Cardiac dysrhythmias associated with an increase in automaticity and a decrease in conduction may result. The relationship between digoxin toxicity and the serum digoxin level is complex; clinical toxicity results from the interactions between digitalis, various electrolyte abnormalities, and their combined effect on the Na^+/K^+ ATPase pump. Cardiac, such as oleander, foxglove, and lily-of-the-valley, is uncommon but potentially lethal. Case reports of toxicity from these sources implicate the preparation of extracts and teas as the usual culprit.

DRUG INTERACTION

Drug interactions are one of the most common causes of digoxin toxicity. Some medications directly increase digoxin plasma levels; other medications alter renal excretion or induce electrolyte abnormalities.

Drugs that have been reported to cause digoxin toxicity include the following:

- ❖ Amiloride - May reduce the inotropic response to digoxin
- ❖ Amiodarone - Reduces renal and nonrenal clearance of digoxin and may have additive effects on the heart rate
- ❖ Benzodiazepines (alprazolam, diazepam) - Have been associated with isolated reports of digoxin toxicity
- ❖ Beta-blockers (propranolol, metoprolol, atenolol) - May have additive effects on the heart rate; carvedilol may increase digoxin blood levels in addition to potentiating its effects on the heart rate
- ❖ Calcium channel blockers - Diltiazem and verapamil increase serum digoxin levels; not all calcium channel blockers share this effect.
- ❖ Cyclosporine - May increase digoxin levels, possibly due to reduced renal excretion
- ❖ Erythromycin, clarithromycin, and tetracyclines - May increase digoxin levels
- ❖ Propafenone - Increases digoxin level; effects are variable.
- ❖ Quinidine - Increases digoxin level substantially but clinical effect is variable; related drugs such as hydroxychloroquine or quinine may also affect levels.
- ❖ Propylthiouracil - May increase digoxin levels by reducing thyroid hormone levels
- ❖ Indomethacin
- ❖ Spironolactone - May interfere with digoxin assays; may directly increase digoxin levels; may alter renal excretion.

- ❖ Hydrochlorothiazide
- ❖ Furosemide and other loop diuretics
- ❖ Triamterene
- ❖ Amphotericin B - May precipitate hypokalemia and subsequent digoxin toxicity
- ❖ Succinylcholine - Increased risk of dysrhythmias has been reported.

Herb/nutraceutical - Avoid ephedra (risk of cardiac stimulation); avoid natural licorice (causes sodium and water retention and increases potassium loss).

Clinical digoxin toxicity represents a complex interaction between digoxin and various electrolyte and renal abnormalities. A patient with normal digoxin levels (0.5-2 ng/mL) but renal insufficiency or severe hypokalemia may have more serious cardiotoxicity than a patient with high digoxin levels and no renal or electrolyte disturbances.

Precautions

In therapeutic doses, digitalis usually produces mild toxic effects. The toxic effects include headache, fatigue, drowsiness, nausea, vomiting and blurred vision. It is therefore, necessary to regulate the dose in such a manner so as to avoid such effects. The toxic effects mentioned should be watched carefully and the dose regulated accordingly.

MECHANISM OF ACTION

Direct Action:

Digitalis binds to the sodium pump¹ on the myocardial cell membrane and inhibits its function. This pump when inhibited causes a rise in the amount of sodium inside the heart cell, which then exchanges it for calcium through the cell membrane, as calcium rises inside the heart cell contractile mechanism becomes more optimal and stronger.

Indirect Action:

Parasympathetic nerve activation results in sinus⁶ node slowing and thus bradycardia. It also inhibits the Atrio-Ventricular Node.

Pharmacokinetics:

Half-life: 1.5 days

Excretion: 60% through kidneys, 30% by the Liver

Body weight is crucial in determining the loading dose, as in a small child with low skeletal muscle mass; less of the loading dose will bind to skeletal muscles and will rather rise the blood digoxin level and cause toxicity.

DIGITALIS USES AND PHARMACOLOGY

Digitoxin is 1,000 times more potent than the powdered leaves and is completely and rapidly absorbed from the gastrointestinal tract. Digoxin is 300 times more potent than the powder prepared from *D. purpurea*. All cardiac glycosides⁷ share the characteristic of improving cardiac conduction, thereby improving the strength of cardiac contractility. These drugs also possess some antiarrhythmic activity, but will induce arrhythmias at

higher dose levels. Digitalis works by inhibiting sodium-potassium ATPase. This results in 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 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 system drive, which is the case with acutely ill persons, and also during exercise.

Congestive heart failure

Digitalis glycosides have been used clinically for the treatment of CHF for more than 200 years.

Animal data

Research reveals no animal data regarding the use of digitalis for CHF.

Clinical data

Numerous studies have been conducted on the use of digitalis as a treatment of CHF in sinus rhythm. The literature identifies a role for digitalis in the treatment of this condition.

Antitumor activity

Recent research has shown the anticancer effects of digitalis compounds, suggesting their possible use in medical oncology.⁹ Further research is needed to see whether cardiac glycosides can be used as antitumor drugs. *D. lanata* and *D. purpurea* were identified as having cytotoxic properties, including cytotoxic activity, and warrant further study. Another study was supportive of investigations showing that apoptosis induction is a major effect of digitalis on several types of tumor cells.⁹ The report demonstrated the anticancer activity of *D. purpurea*. *L. heywoodii* on 3 human cancer cell lines. The results of one study revealed marked differences in cytotoxicity between the cardiac glycosides, both in potency and selectivity, and modes of action that differ from those of commonly used anticancer drugs. More studies are needed to clarify a possible role of cardiac glycosides in chemotherapy of malignant diseases.

Animal data

Short-term animal experiments concluded that toxic doses would be needed to produce an anticancer effect in humans. However, susceptibility for cardiac glycosides differs between species, indicating that the results from animal models cannot be extrapolated into humans.

Clinical data

Several investigators have postulated that digitalis glycosides could be used in cancer therapy, and that they may operate through novel mechanisms; however, this idea has not found wide acceptance.

DOSAGE

Digitalis leaf provides a narrow therapeutic index, requiring close medical supervision for safe use. Classical dosage started at 1.5 g of leaf divided between 2 daily doses. Purified digoxin is typically used at daily doses of 0.125 to 0.25 mg.

DIGITALIS TOXICITY

All parts of the plant are toxic. Animal toxicity occurs during grazing. Children have been made ill by sucking the flowers or ingesting seeds or parts of the leaves. Deaths have been reported among persons who drank tea made from digitalis mistakenly identified for comfrey, although the bitter taste often deters ingestion or its emetic properties can induce vomiting. Digitalis glycosides are excreted slowly and accumulate; therefore, intoxications during therapy are common. The incidence of digitalis toxicity has been estimated to range from 5% to 23%. More stringent dosing guidelines and monitoring techniques have dramatically reduced the incidence of therapeutic overdose. Digitalis poisoning often is associated with intentional ingestion by adolescents and adults, sometimes with suicidal intent. Signs of poisoning by the plant or purified drug include contracted pupils, blurred vision, strong but slowed pulse, nausea, vomiting, dizziness, excessive urination, fatigue, muscle weakness, and tremors; in severe cases, stupor, confusion, convulsions, and death occur. Cardiac signs include atrial arrhythmias and atrioventricular block. The cardiac effects are the most dangerous. Chronic⁴ digitalis intoxication⁵ is characterized by visual halos, yellow-green vision, and gastrointestinal upset. In mild cases of toxicity (atrial fibrillation with a slow ventricular response or occasional ectopic beats), temporary withdrawal of the drug and electrocardiogram monitoring is sufficient. Gastric lavage or emesis together with supportive measures, such as electrolyte replacements, antiarrhythmics (eg, lidocaine, phenytoin), atropine, and other agents that can antagonize the cardiovascular effects of the glycosides, have been used to manage acute poisonings. Digoxin-specific Fab antibody fragments¹⁴ (Digibind) are effective in managing acute intoxications caused by digitalis and related cardioactive glycosides. This therapy is revolutionary for the severely poisoned patient. Digoxin Fab fragment antibodies by infusion are an effective antidote for some plant cardiac glycosides¹⁵, but not always for digitalis.

CONCLUSION

Digitalis is of great value in chronic valvular cardiac disease, with failing or broken compensation, but it must be used with judgment, observing the need in the weak, fast, and irregular pulse, deficient urination, and dropsy. When hypertrophy of the heart overbalances dilatation, and evidences of arterial hyperaemia are present, digitalis is likely to aggravate the condition, or otherwise do harm. Digitalis medication is most effective probably in mitral insufficiency, with regurgitation, provided there are no pericardial adhesions restraining its effects, or advanced myocardial degeneration. It overcomes the ventricular strain dependent upon pulmonic vascular resistance, and helps, by contracting the ventricle rings, to attain a more perfect closure of the mitral valves. The main way it

achieves this function is through increasing myocardial contractility¹⁶. The World Health Organization (WHO) estimates that 4 billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care. Herbal medicine is a major component in all indigenous peoples' traditional medicine and a common element in Ayurvedic, homeopathic, naturopathic, traditional oriental¹⁷. The digitalis drugs come in many forms, differing in their chemical structure^{18,19}.

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REFERENCES

1. Bagrov, A.Y., Fedorova, O.V (2005). Cardenolide and bufadienolide ligands of the sodium pump. How they work together in NaCl sensitive hypertension. *Front Biosci* Vol.10: 2250-2256.
2. Buckalew, V.M (2005). Endogenous digitalis-like factors. An historical overview. *Front Biosci* 1, Vol.0:2325-2334.
3. Blaustein, M.P., Zhang, J., Chen, L., Hamilton, B.P (2006). How does salt retention raise blood pressure? *Am J Physiol Regul Integr Comp Physiol*; Vol.290:R514-R523.
4. Dec GW (2003). Digoxin remains useful in the management of chronic heart failure. *Med Clin North Am* .Vol.87:317-337.
5. Dick M, Curwin J, Tepper D (1991). Digitalis intoxication recognition and management. *J Clin Pharmacol* .Vol.31:444-447.
6. Hood WB, Dans A, Guyatt GH, Jaeschke R, McMurray JJ(2004). Digitalis for treatment of congestive heart failure in patients in sinus rhythm. *Cochrane Database Syst Rev* (2):CD002901.
7. Johansson S, Lindholm P, Gullbo J, Larsson R, Bohlin L, Cleason P(2001). Cytotoxicity of digitoxin and related cardiac glycosides in human tumor cells. *Anticancer Drugs*. Vol. 12:475-483.
8. Lopez-Lazaro M, Palma De La Pena N, Pastor N, et al(2003). Anti-tumour activity of Digitalis purpurea L. subsp. heywoodii. *Planta Med* .Vol.69:701-704.
9. Lindholm P, Gullbo J, Claeson P, et al(2002). Selective cytotoxicity evaluation in anticancer drug screening of fractionated plant extracts. *J Biomol Screen* . Vol.7:333-340.
10. Lacassie E, Marquet P, Martin-Dupont S, Gaulier JM, Lachatre G(2000). A non-fatal case of intoxication with foxglove, documented by means of liquid chromatography-electrospray-mass-spectrometry. *J Forensic Sci* .Vol.45:1154-1158.
11. Meyer JE (2002). *The Herbalist*. Hammond, IN: Hammond Book Co; 1934: 96.

- Belcastro PF. Digitalis: from folklore remedy to valuable drug. *J Am Pharm Assoc.* Vol. 42:857.
12. McGuffin M, Hobbs C, Upton R, Goldberg A, eds (1997). *American Herbal Products Association's Botanical Safety Handbook*. Boca Raton, FL: CRC Press.
 13. Nesher, M., Spolansky, U., Rosen, H. and Lichtstein, D(2007). The endogenous digitalis- like compounds - A new family of steroid hormones. *Life Sci.* Vol.80:2093- 2107.
 14. Shumaik GM, Wu AW, Ping AC (1988). Oleander poisoning: treatment with digoxin-specific Fab antibody fragments. *Ann Emerg Med.* Vol.17:732-735.
 15. Schoner, W (2002). Endogenous cardiac glycosides, a new class of steroid hormones. *Eur J Biochem* Vol.269:2440-2448.
 16. Schoner, W., Bauer, N., Muller-Ehmsen, J., Kramer, U., Hambarchian, N., Schwinger, R., Moeller, H., Kost, H., Weitkamp, C., Schweitzer, T., Kirch, U., Neu, H., Grunbaum, E.G (2003). Ouabain as a mammalian hormone. *Ann N Y Acad Sci.* Vol.986:678-684.
 17. Schoner, W. and Scheiner-Bobis, G (2007). Endogenous and exogenous cardiac glycosides and their mechanisms of action. *Am J Cardiovasc Drugs.* Vol.7:173-189.
 18. Tatro DS, ed. *Drug Interaction Facts*. St. Louis, MO(2002): Wolters Kluwer Health, Inc.; 2004. Jowett N. Foxglove poisoning. *Hosp Med.* Vol.63:758-759.
 19. Wickersham RM, Novak K (2004), managing eds. *Drug Facts and Comparisons*. St. Louis, MO: Facts and Comparisons.
