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Digitalis Historical Background and Current Status

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Abstract: *The earliest recorded treatment of digitalis is typically credited to William Witherings investigation on the foxglove, which was published in 1785. The rich background of digitalis is intriguing. Yet, there is evidence of some awareness of herbs used for remedies for heart failure with complications that have effects similar to those of digitalis dating back to roman times. In relation to this, the foxglove's natural components (Digitalis purpurea and Digitalis lanata) also include ouabain, a quick-acting glycoside typically derived from Strophanthus gratus. These substances are known as cardiotonic steroids. These medications are effective sodium-potassium adenosine triphosphatase antagonists. Digitalis as well as its metabolites, specifically digoxin, served as the gold standard of treatment for CHF during the duration of the 20th century. As the century came to a close, however, several concerns—particularly those related to ensuring enhanced safety—were raised regarding their usage as additional therapies for CHF, such as lowering the left ventricle's preload. An important medication used to treat cardiac arrhythmias and high blood pressure is still digitalis glycosides. The properties of the all cardioactive glycosides enhance the myocardial fibre contractile strength in a manner that is similar. Almost 100% of digoxin is absorbed, has a $T^{1/2}$ life of 5 to 7 days, and is mainly excreted in the urine as cardioinactive metabolites with just 8% of it being converted to digoxin. The inhibition of membrane Na^+/K^+ ATPase and its resulting impacts on calcium movement are thought to be the reason behind this. Digitalis and certain medications can interact, most commonly with diuretics that cause hypokalaemia or hypomagnesaemia. The management of cardiac arrhythmias following digitalis toxicity is mainly possible by favourable interactions with antiarrhythmic pharmaceuticals (lignocaine, phenytoin), however the efficiency of other medications, such propranolol, is occasionally constrained by their adverse inotropic effects.*

Keywords: Digitalis, digitalis pharmacokinetics, Pharmacological actions, digitalis adulterants, digitalis toxicities

I. INTRODUCTION

The majority of medical professionals, including those who are familiar with medical history, attribute the discovery of digitalis to William Withering. For thousands of years, digitalis glycosides and other herbs with equivalent to cardiotonic properties have been used to cure human disease. [1] The treatment of heart failure with cardiac glycosides and have beneficial inotropic effects, although they are usually recommended. The increase in intracellular Ca^{2+} that causes their inotropic effect also produces the cause of cardiac glycoside intoxication-related arrhythmias. The atrioventricular node's Ca^{2+} current is inhibited by these medicines' substantial vagotomic effects, which also cause the atrium's acetylcholine-mediated K^+ currents to be stimulated. [2] The primary "indirect" electrophysiological impact of cardiac glycosides shows the hyperpolarization, reduction in the atrial action potential's, and enhanced atrioventricular nodal refractoriness. Digoxin's effectiveness in stopping re-entrant arrhythmias involving the atrioventricular node and in regulating ventricular response in atrial fibrillation patients can be attributed to the last activity. Given that many of these patients have cardiovascular disease, which can be made worse by other atrioventricular nodal blocking

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medications such Ca^{2+} channel blockers cardiac glycosides may be especially helpful in the final case. Digitalis is not particularly successful in lowering the rate, however, as many patients with severe heart failure have considerably enhanced sympathetic drive. .[3] The only treatment that may have a little chance of lowering the pace is digitalis therapy. Cardiac glycosides do not control heart rate. Digitalis can cause alterations in automaticity and delayed following depolarization, which can be amplified by increased sympathetic activity and hypoxia, raising the risk of digitalis poisoning. [4]

1.1 Pharmacokinetics of Digoxin

Digoxin pills have a 75% bioavailability rate and are only partially absorbed. Digoxin's bioavailability may be significantly decreased in certain people by intestinal microflora's capacity to metabolise the drug. For clinical success in these individuals, higher-than-usual dosages are necessary; toxicity is a significant danger if antibiotics that kill gut microbiota are used. Another potential contributing factor to toxicity is P-glycoprotein inhibition. 20% to 30% of digoxin is protein-bound.[5] Even with intravenous therapy, there is a period of many hours administration of medication and the formation of the ventricular rate in atrial fibrillation because the antiarrhythmic effect diffuse to the target location of digoxin relatively slowly . A loading dosage of around 0.6 mg to 1 mg digoxin is given over the course of 24 hours to prevent intoxication. [6] Although there is a larger risk of side effects, some people may need and tolerate higher dosages. Digoxin usually has a 36-hour elimination half-life in humans, thus maintaining dosages are given once daily. Digoxin is eliminated mostly (80%) by renal clearance of unaffected drugs. Digoxin is mostly metabolised in the liver and may be helpful for people with chronic or severe renal impairment. Drugs that promote hepatic metabolism, such as phenytoin and rifampin, speed up the metabolism of digitoxin.[7] Digoxin, quinidine, diltiazem, cyclosporine, , and flecainide reduce the clearance of digoxin, probably by blocking P-glycoprotein, which is the main method of digoxin elimination. When quinidine or digoxin are begun, the dose of digoxin is often decreased since digitalis toxicity occurs so frequently with these medications. The dosage should always be adjusted as needed based on the results of routine digoxin concentration measurements. [8]

Table 1: Comparative pharmacokinetic of Digoxin and Digitoxin

Parameters	**Digoxin**	**Digitoxin**
Source	*Digitalis lanata*	*Digitalis Purpurea*
Absorption	60-80%	80-90%
PPB	25%	75%
Vd	Vd 38 L/70 kg	500 L/70 kg
Elimination	Hepatic metabolism	Renal excretion (by glomerular
$T^{1/2}$	40hours	6-7 Days
Toxic concentration	> 35 ng/mL	> 2 ng/mL

1.2 Digitalis Glycosides for Clinical Use

There are several cardiac glycosides that fall under the category of cardiotonic steroids, and ouabain. Cardiac glycosides, demonstrated potential in the treatment of cancer, particularly leukaemia. [9] Cardiac glycosides all have a specific affinity to sodium–potassium adenosine triphosphatase. After binding, these cardiac glycosides become extremely particular inhibitors of the Na^+/K^+-ATPase found in cellular membranes, also known as the "cellular sodium pump," which connects membrane ion translocation with high-energy ATP hydrolysis. [10] Cardiac glycosides exhibit functional diversity, exhibiting a range of characteristics and therapeutic uses. [11]Digitalis leaf (prepared digitalis) is a raw combination of glycosides, however the activity of each tablet formulation may vary made from powdered foxglove leaves that needs biological standardisation.The white foxglove, *Digitalis lanata*, is the source of lanatoside-C, the glycoside precursor to digoxin, as well as digoxin, the most common digitalis derivative. [12] While it may be made from other plant sources, ouabain, another pure glycoside, is typically obtained from Strophanthus gratus. Because of its quick beginning of action, which has previously been thought to be beneficial, some doctors believe ouabain to be particularly effective. [13]

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1.3 Digitalis Glycosides' Therapeutic Potential in New Medicine

In plants, animals, and insects, there are endogenous cardiac glycosides made from a simple sugar and another substance created when a hydroxyl group in the sugar molecule is changed. Our knowledge of digitalis derivatives and their use as medicines is complicated by these substances' prevalance. The substance, ouabain, is really an endogenous hormone with a role in modulating the Na^+/K^+-ATPase activity in renal tubular cells.[14] Both ouabain and digoxin are cardiotonic steroids that have been found in the blood plasma, hypothalamus, and adrenal glands of mammals.[16] Exercise may improve heart function by causing fast changes in endogenous ouabain, which raises the intracellular calcium level in atrial and myocardial cells.[17] In addition, elevated levels of endogenous ouabain have been linked to cardiac hypertrophy, cardiac dysfunction, and arterial hypertension. For example, 40% of Europeans with uncomplicated hypertension were found to have elevated levels of endogenous ouabain in conjunction with cardiac hypertrophy and a decreased heart rate, whereas elevated levels of endogenous ouabain in advanced hypertension were linked to blood pressure and total peripheral resistance. [18] Those with idiopathic dilated cardiomyopathy who are more prone to have CHF advance also had higher levels of endogenous ouabain. Rostafuroxin, an endogenous ouabain antagonist, has been shown to lower blood pressure in hypertensive animals, and it may represent a new class of antihypertensive drugs that function by blocking ouabain at the Na^+/K^+-ATPase pump. [19] It's important to note that digitalis-like substances have been shown to be higher in preeclampsia patients in relation to endogenous cardiac glycosides, which have been linked to hypertension. Using digoxin-binding antibodies demonstrated to reduce the incidence of pulmonary edema and worsening in renal function in women with severe preeclampsia who are far from term. [20]

1.4 Herbal Adulterants Causes Digitalis Toxicity

Some people use boiling comfrey leaves as herbal remedy for insomnia, which raises an intriguing toxicity issue. It appears that when the foxglove (*D. Purpurea) is*not in flower, the leaves of comfrey (*Symphytum ofcinale*) and foxglove are readily mistaken. [21] As in the case of nine patients who presented with nausea, vomiting, diarrhoea, and dizziness and whose peak serum digoxin levels ranged from to 139.5 ng/ml, outbreaks of foxglove poisoning have been reported when the intention was to consume a comfrey herbal tea. These patients were treated with digoxin-binding antibodies.The cardiac glycosides found in the plant, such as digoxin and digitoxin, cause digitalis poisoning when the leaves of foxglove are processed and consumed.[22] In one such instance, the consumption of foxglove leaves inadvertently was verified by a raised blood digoxin level, and therapy with digoxin-binding antibodies was effective.In another instance, three patients ate potato dumplings flavoured with leaves of *Borago ofcinalis* that were mistakenly mixed in with leaves of *D. Purpurea*, the foxglove. [22] In addition to foxglove species, cardiac glycosides are found in different plants all over the world. For instance, a case report described the intake of an extract from the Indian rubber vine plant that caused digitalis poisoning (*Cryptostegia grandifora*) [23]Since an ingredient like this cannot be classified as a drug until the pharmaceutical company demonstrates its efficacy and safety, the transformation of digitalis from foxglove as a traditional remedy to a contemporary pharmaceutical highlights the significance of regulation. It is up to the US FDA to prove the supplement is dangerous when it is still being used as a nutritional supplement or as a herbal medicine, both of which can be abused. [25]

1.5 Digoxin and Herbal Interactions

It is always a worry when a medication, like digoxin taken for a particular purpose, interacts unexpectedly with another medication. Medical professionals must be conscious of and record such utilization because anywhere between 18 and 45% of patients may also be taking an alternative, supplemental, or herbal medication. [26] For instance, digoxin's plasma or blood concentration can be reduced due to cytochrome P450 (CYP) and Digoxin and SJW P-glycoprotein (PgP) relationship [27] in actuality, CYP3A4 is the one that is so strongly stimulated by SJW, and both SJW and digoxin are CYP3A4 and PgP substrates. Other popular supplements like ginkgo, ginseng, kava, and saw palmetto have no effect on the blood amount of digoxin. Digoxin toxicity has been linked to discontinuing an SJW herbal drink in patients who were already taking the drug. [28]

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1.6 Digitalis as an Anticancer Agent

Digitalis is being studied as a potential protective medication. Digoxin, digitoxin, and ouabain are examples of digitalis cardiac glycosides that have been shown in a research of prostate cancer cell lines to inhibit the growth of these cancerous cell lines, though the sensitivity of the three cell lines varied. Increased apoptosis and a prolonged rise in Ca^{2+} concentration in the cells are two potential inhibitors of prostate cancer cells. [29] Additionally, it has been proposed that activation of Na^{+}/K^{+}-ATPase, a recognized side effect of digitalis preparations, could serve as novel target for cancer treatments to enhance therapeutic effects.[30] Due to its estrogen-like action, cardiac glycosides may specifically raise the risk of some cancers. Additionally, the antitumor action of digitalis observed in preclinical studies needed high digitalis concentrations that would not be tolerated in the normal clinical scenario.[31] Additionally, demonstrated that digitalis glycosides have positive effects on a variety of cancer cell lines, including the kidney adenocarcinoma cancer cell line in specific. The anticancer of digitalis is most likely caused by death of cell.

1.7 Pharmacological Action of Digitalis-

- Positive inotropic action by which it increases the contraction by increasing intracellular Calcium ions.
- Decreases Heart rate by increasing vagal tone and decreases sympathetic overactivity by increasing SA Node and AV node activation.
- No significant changes on blood pressure
- Increase blood circulation towards kidney result in better renal perfusion which leads to normal diuresis. [32]

II. CONCLUSION

The William Withering-developed foxglove derivatives of digitalis, particularly digoxin, still have a position in clinical cardiology, despite current debate and unease about their use, particularly by younger doctors. However, competent and devoted clinicians who will closely watch digoxin serum levels must use this medication. The safest digoxin levels appear to be ≤ 1.0 ng/ ml, with no advantage from higher levels. The narrow therapeutic window means that experience and skill are required for the use of digoxin. It is most doubtful that any meta-analysis or observational study are sufficiently controlled or will be able to control for these precise variables. The strongest case for the use of digoxin is when rate control is intended for a patient with atrial fibrillation (AF) who also has a rapid ventricular response and concurrent relative hypotension, as all other rate-controlling drugs like metoprolol, diltiazem, and verapamil lower blood pressure.However, when used precisely, it also appears suitable for a small number of doctors to keep in mind and use the foxglove as an additional treatment for CHF when the desired clinical state is not achieved. Overall the use of digitalis is currently limited although the major cardiac disorder being treated with digitalis. The availability of newly discovered therapeutic agents, toxicity of digitalis, safety concerns and adulterants are the primary reason for limited use of digitalis.

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