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THE HEART MEDICATION DERIVED FRON THE FOXGLOVE PLANT

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ABSTRACT

Digoxin, a cardenolide cardiac glycoside extracted from Digitalis lanata and D. purpurea (foxglove), exemplifies the fusion of herbal tradition and modern pharmacology in treating heart failure with reduced ejection fraction (HFrEF) and atrial fibrillation (AF). Isolated in 1930, its steroidal aglycone (digitoxigenin) with trisaccharide chain inhibits Na+/K+-ATPase, elevating intracellular Ca^{2+} for positive inotropy (+20-30% contractility) and vagal AV nodal slowing (rate control, ↓20-40 bpm). The DIG trial confirmed reduced HF hospitalizations (28% RR 0.72) without mortality benefit, positioning it as GDMT adjunct (target 0.5-0.9 ng/mL). Historically, William Withering's 1785 monograph standardized "dropsy" remedies from folklore. Chemically ($C_{41}H_{64}O_{14}$, MW 780.94), industrial ethanol extraction from year-2 leaves (0.3-0.8% yield) yields HPLC-purified API, with amphipathic properties aiding GI absorption (renal clearance 60-80%, t½ 36-48h). Clinical uses include symptomatic HFrEF (NYHA II-IV) and sedentary AF rate control. Toxicity (narrow index) manifests as GI (nausea), visual xanthopsia, and arrhythmias (bidirectional VT), exacerbated by hypoK, renal impairment, or P-gp inhibitors; DigiFab reverses severe cases. Pharmacognosy ensures standardization via microscopy, HPTLC/HPLC (≥95% purity), and ICH stability. Ongoing biotech (e.g., DBH cloning) enhances sustainable production, while nanoparticles address bioavailability. Digoxin's legacy underscores natural product rigor, pharmacogenomics, and precision cardiology amid rising CVD burdens.

KEYWORDS: Digoxin, cardiac glycoside, foxglove, heart failure, atrial fibrillation.

INTRODUCTION

Digoxin, the quintessential heart medication derived from the foxglove plant (Digitalis purpurea and Digitalis lanata), stands as a testament to the enduring bridge between herbal folklore and modern pharmacology. This cardiac glycoside, first harnessed for its life-saving potential in treating congestive heart failure and atrial fibrillation, exemplifies how nature's bounty can yield potent therapeutics when guided by scientific rigor. At its core, digoxin's mechanism revolves around the inhibition of the sodium-potassium ATPase pump on cardiac myocytes, a pivotal action that disrupts ion gradients to foster increased intracellular calcium. This elevation enhances myocardial contractility—termed the positive inotropic effect—bolstering the force of each heartbeat without excessively raising oxygen demand, a boon for failing hearts strained by systolic dysfunction. Simultaneously, its vagomimetic properties prolong the refractory period at the atrioventricular (AV) node, curbing rapid ventricular responses in tachyarrhythmias like atrial fibrillation, thus restoring hemodynamic stability.

The clinical relevance of digoxin persists into the 21st century, despite the advent of more tolerable agents like beta-blockers, ACE inhibitors, and SGLT2 inhibitors. Current ACC/AHA guidelines position it as an adjunct for persistent heart failure symptoms in HFrEF (heart failure with reduced ejection fraction), particularly when hospitalization risk looms large, as evidenced by the landmark DIG trial demonstrating a 28% reduction in such events, albeit without mortality benefit. In atrial fibrillation, it excels for rate control in sedentary patients or those intolerant to first-line options, though its role has waned amid evidence of neutral or adverse outcomes in certain subgroups. Pharmacokinetically, digoxin's renal clearance (60-80%) and enterohepatic recirculation confer a half-life of 36-48 hours in normals, extending to days in renal impairment—necessitating therapeutic drug monitoring targeting 0.5-0.9 ng/mL to sidestep toxicity. This narrow therapeutic index, a hallmark since its inception, amplifies risks of nausea, visual xanthopsia (yellow-tinted vision), and bidirectional ventricular tachycardia, with hyperkalemia signaling severe overdose treatable via digoxin-specific Fab antibodies.

Beyond efficacy, digoxin's journey illuminates pharmaceutical evolution: from crude leaf infusions to crystalline purity, it pioneered bioavailability standardization and laid groundwork for quality-by-design principles in botanicals. Its steroidal aglycone structure, adorned with sugar moieties, inspires synthetic analogs and informs research into next-generation inotropes for advanced therapies like mechanical circulatory support. Yet challenges abound—P-glycoprotein interactions with common drugs (e.g., verapamil, amiodarone) heighten exposure, while hypokalemia or hypothyroidism potentiate arrhythmias. In an era of precision medicine, pharmacogenomics reveals CYP3A4 and ABCB1 variants modulating response, urging tailored use.

For pharmacy scholars and formulation scientists, digoxin embodies natural product chemistry's gold standard: extraction via ethanol-water solvents yields glycosides amenable to HPLC quantification and stability studies under ICH guidelines. Its legacy underscores regulatory vigilance—from Withering's empirical dosing to FDA's Lanoxin labeling—and fuels ongoing inquiries into nanoparticle encapsulation for bioavailability enhancement or repurposing in cancers exploiting Na/K-ATPase overexpression. As heart disease burdens global health, digoxin's renaissance beckons, blending tradition with innovation to affirm foxglove's cardiac sovereignty.

Fig no.1. Foxglove Plant.

Historical Background

Foxglove's medicinal legacy predates written records, with European herbalists in the Middle Ages employing Digitalis purpurea leaf infusions to alleviate "dropsy"—the edema signaling congestive heart failure. Welsh physicians, for instance, documented its use in the 13th century for urinary disorders linked to cardiac decompensation, while Roman and Greek texts allude to similar purple-flowered plants for swellings. These empirical applications persisted through the Renaissance, often as teas or poultices, though toxicity curtailed widespread adoption amid unpredictable dosing from variable plant glycoside content.

The modern era dawned in 1775 when English physician William Withering encountered an old Shropshire woman whose herbal tea cured a patient of dropsy after conventional therapies failed. Intrigued, Withering embarked on a decade-long systematic study, culminating in his landmark 1785 monograph An Account of the Foxglove, and Some of Its Medical Uses: With Practical Remarks on the Digitalis, and an Appendix Containing Some Precepts of Diet and Regimen. Tracking 158 patients, he reported relief in 101, with precise observations on efficacy (diuresis, pulse slowing) and perils (nausea, vomiting, visual halos, bradycardia). Withering pioneered standardization—drying leaves at low heat, infusing in boiling water, and titrating to just below toxicity—achieving doses akin to modern digoxin equivalents (0.5-1 mg daily). His work elevated digitalis from superstition to rational pharmacology, admonishing: "Much mischief has been produced by indiscriminate use."

19th-century refinements followed: French apothecary Pierre Louis quantified digitalis leaf activity in 1819, while chemists isolated digitoxin (from D. purpurea) in 1872 and gitoxin. The 20th century brought purity—Sydney Smith crystallized digoxin in 1930 from D. lanata (richer in this glycoside), enabling injectable and tablet forms. Burroughs Wellcome launched Lanoxin in 1934, with FDA approval for heart failure in 1998 (post-DIG trial) and atrial fibrillation rate control. Civil War surgeons like Jonathan Letterman lauded it for battlefield shock, and Victorian physicians integrated it into "digitalis therapy" protocols.

Chemistry

Chemically, digoxin is a cardenolide-type cardiac glycoside with the molecular formula $C_{41}H_{64}O_{14}$ and a molecular weight of 780.94 g/mol. Its core is a hydrophobic steroidal aglycone (genin) termed digitoxigenin—a cyclopentanoperhydrophenanthrene (gonane) nucleus featuring hydroxyl (-OH) groups at C-3 (axial), C-12 (equatorial), and C-14 (beta), plus a β-glycosidic linkage at C-3 to a trisaccharide moiety. This hydrophilic chain comprises three 2,6-dideoxy-3-O-methyl-hexose units (digitoxoses, each with a methyl ether), rendering the molecule amphipathic for membrane interaction. The hallmark is the α,β-unsaturated butyrolactone (butenolide) ring fused at C-17, conferring high affinity for Na+/K+ ATPase via hydrogen bonding and van der Waals forces.

Biosynthesis in foxglove occurs via mevalonate pathways, yielding protoveratrine precursors acetylated to cardenolides (0.2-0.5% dry leaf weight). Industrial extraction employs ethanol-water maceration (70:30), filtration, and chromatography, with D. lanata preferred over D. purpurea for higher digoxin (vs. digitoxin) yield. Purification via silica gel chromatography or recrystallization yields white, odorless prisms (mp 235-240°C), sparingly soluble in water (50 mg/L) but freely in methanol/DMSO, with logP ~1.26 indicating balanced lipophilicity for GI absorption. Unlike lipid-soluble digitoxin (no C-12 OH), digoxin's tertiary alcohol accelerates phase II metabolism (glucuronidation/sulfation) and renal clearance. Spectroscopically, it shows IR peaks at 3400 cm^{-1} (O-H), 1770 cm^{-1} (lactone C=O), and NMR singlets for digitoxose methyls (δ 1.2 ppm); HPLC-UV (220 nm) or LC-MS/MS assays ensure 99% purity per USP monographs, stable at pH 6-7 (ICH Q1A: <5% degradation/6 months at 25°C/60% RH). Formulation challenges include P-gp efflux mitigation via amorphous dispersions or nanoparticles.

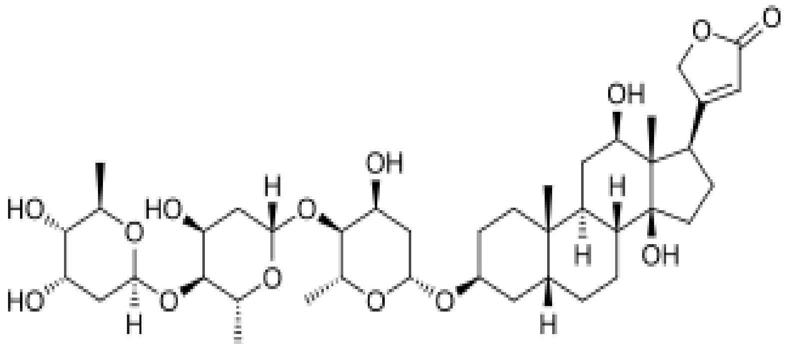

Fig.no.2. Molecular structure of Digoxin.

Mechanism of Action

Digoxin's primary target is the α-subunit of sarcolemmal Na+/K+ ATPase, binding to the E2-P extracellular conformation (K_d ~10^{-8} M) with isoform selectivity: cardiac α2/α3 over ubiquitous α1. Inhibition halts the $3Na^+$ efflux/$2K^+$ influx cycle, raising cytosolic $[Na^+]_i$ from 10 to 20 mM. This attenuates the electrochemical gradient for the Na^+/Ca^{2+} exchanger (NCX1, $3Na^+$ in/$1Ca^{2+}$ out), shifting it toward reverse mode (Ca^{2+} entry) and curbing forward extrusion. Net $[Ca^{2+}]_i$ rises 20-50%, saturating calsequestrin in sarcoplasmic reticulum (SR); ryanodine receptor (RyR2) release during systole floods myofibrils, prolonging troponin C-Ca^{2+} binding, actin exposure, myosin cross-bridges, and ejection fraction (+20-30% inotropy without ↑O_2 use).

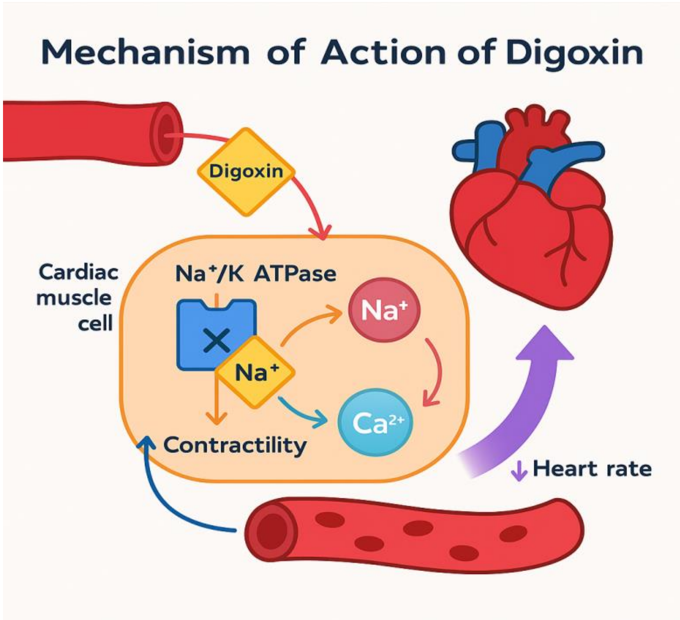

Fig.no.3.Mechanism of Action of Digoxin.

Vagally, digoxin sensitizes arterial baroreceptors, boosting afferent C-fiber firing to nucleus tractus solitarius, enhancing cardiovagal outflow via choline acetyltransferase. This hyperpolarizes AV nodal Purkinje cells (↑K^+ conductance, I_KACh), prolonging AH interval (negative dromotropy, -25% conduction velocity) for rate control in AF (↓ ventricular response 20-40 bpm). Sympathetic withdrawal yields negative chronotropy at SA node (↓I_f funny current). Indirectly, ↑$[Ca^{2+}]_i$ upregulates SERCA2a via phospholamban phosphorylation, optimizing diastolic relaxation.

At toxic levels (>2 ng/mL), delayed afterdepolarizations (DADs) from SR Ca^{2+} overload trigger triggered activity (e.g., bidirectional VT). Non-cardiac effects include P-gp inhibition (↑verapamil levels) and anti-proliferative Na/K-ATPase signaling in cancers. Therapeutic window (0.5-0.9 ng/mL) demands TDM, with pharmacogenomics (ABCB1 3435C>T) guiding dosing.

Clinical uses

Heart Failure with Reduced Ejection Fraction (HFrEF)

In stage C HFrEF (LVEF ≤40%), digoxin is recommended (class IIa) for persistent symptoms (NYHA II-IV) or frequent hospitalizations despite guideline-directed medical therapy (GDMT: ARNI/ACEI/ARB, beta-blockers, MRA, SGLT2i). The landmark DIG trial (n=6,800, 1997) reported no overall mortality reduction (RR 0.99) but a 28% decrease in HF hospitalizations (RR 0.72; p<0.001), with subgroup benefits in LVEF <25% (RR 0.76

hospitalizations), cardiothoracic ratio >0.55 (RR 0.65), or low EF + enlarged heart (RR 0.46). PROVED and RADIANCE trials confirmed symptom relief and reduced hospitalizations at lower serum levels (0.5-1.0 ng/mL). It enhances exercise capacity (6-minute walk +30-50m), LV function (↑EF 2-4%), and quality of life (MLHFQ score ↓10-15 points), acting via Na+/K+ ATPase inhibition without elevating myocardial O_2 demand. Optimal dosing: load 0.5-1 mg (divided), maintenance 0.125-0.25 mg QD, adjusted for CrCl <50 mL/min (0.0625-0.125 mg); target trough 0.5-0.9 ng/mL to minimize harm (levels >1.2 ng/mL raise mortality 20-50%).

Atrial Fibrillation (Rate Control)

Digoxin controls ventricular response in persistent/permanent AF (class IIa, first-line in sedentary/elderly or IIb with beta-blockers), slowing AV nodal conduction via increased vagal tone (↓HR 20-40 bpm at rest). AFFIRM subgroup (2002) and meta-analyses (e.g., 2018) show superior symptom control vs. diltiazem in some cohorts, though inferior during exertion (exercise HR ↓15-25 bpm vs. 40 bpm for BB/CCB). Preferred in hypotension, COPD, or HF comorbidity; IV loading (0.5 mg q6h x3) for acute control. Recent data (2024) reaffirm safety in sinus rhythm conversion post-rate control.

Toxicity and Safety Concerns

Clinical Manifestations

Gastrointestinal (GI): Earliest and most frequent (60-80% of symptomatic cases), driven by direct enterocyte irritation and area postrema chemoreceptor trigger zone (CTZ) activation via D2 dopamine antagonism. Symptoms include progressive anorexia (first sign), intractable nausea/vomiting (central + peripheral emetic pathways), epigastric pain (mucosal ischemia), diarrhea (serotonin release), or ileus/constipation (autonomic imbalance). Unlike food poisoning, vomiting lacks fecal odor and persists >24h; endoscopy may show nonspecific gastritis. In overdose, hemorrhagic enteritis occurs in 10-15%.

Neurologic/Visual

Dose-dependent CNS penetration (10-30% BBB crossing) yields fatigue (80%), disorientation, confusion (50%), drowsiness, or delirium (hallucinations, agitation in 15%). Seizures rare (5%, severe hyperK). Ocular hallmarks from retinal rod/cone Na/K ATPase inhibition: xanthopsia (yellowish vision/halos around lights, 25-50%), chromatopsia (objects appear green/yellow), photophobia, scotomas (central/paracentral), blurred vision, diplopia, or blindness (reversible). Fundoscopy reveals retinal edema; classic but only 15% sensitivity—prompts "Is it digitalis?" mnemonic.

Cardiac (90% severe toxicity; 50% fatalities)

Increased automaticity (ectopics) + decreased conduction (blocks) yield "paralyzing arrhythmia" spectrum: sinus bradycardia (<50 bpm), SA arrest, 1°-3° AV block (Wenckebach/Mobitz), junctional/ventricular escape rhythms (50-100 bpm), accelerated junctional tachycardia (AJT), nonparoxysmal junctional tachycardia (NPJT), atrial tachycardia with block (ATwB, "poor man's flutter"), PVCs/bigeminy, bidirectional VT (pathognomonic; alternating QRS axis via fascicular alternation), torsades (Ca overload), VT/VF. ECG: downsloping "scooped" ST depression (Salvador Dali mustache), flat/inverted T-waves, prominent U-waves, short QT, Osborne J-waves, low voltage. Acute: hyperkalemia (>5.5 mEq/L, peaked T); chronic: hypokalemia unmasking.

Table.no.1. Toxicity Manifestations by System.

System	Early Signs	Severe Signs
GI	Anorexia, nausea	Vomiting, pain
Visual	Yellow halos	Scotomas, blindness
Cardiac	Bradycardia, PVCs	Bidirectional VT, VF

Endocrine/Metabolic/Other

Gynecomastia/tender breasts (chronic, estrogen-like), thrombocytopenia (<100k), maculopapular rash (10%), eosinophilia. Acute intoxication shifts RBC Na/K ATPase inhibition → hyperkalemia (K efflux block); chronic mimics hypoK effects.

Risk Factors and Predictors (Extended)

Demographic: Elderly >70y (OR 2.7-4.0; ↓CrCl, polypharmacy), low BW <60kg (↑levels 50%), females (higher bioavailability), infants/children (sensitive myocardium). Comorbidities: CKD stage 3+ (levels ↑2-5x; CrCl <30 halves dose), hypothyroidism (↓clearance 30%), hypoxia/acidosis (↑binding), amyloidosis. Electrolyte: HypoK <3.5 mEq/L (5-10x toxicity risk; competes for ATPase), hypoMg <1.7 mg/dL (blocks K repletion), hyperCa >12 mg/dL ("stone heart"—tetany/asystole). Pharmacologic: P-gp inhibitors (amiodarone ↑100-200%, verapamil ↑300-600%, dronedarone, itraconazole, ritonavir), loop/thiazides (hypoK), rifampin (↓levels). DIG post-hoc: levels >1.2 ng/mL HR 1.46 (all-cause), >2.0 HR 2.04; >3.0 near-certain fatality untreated.

Diagnosis and Severity Scoring

Gold standard: serum digoxin ≥6h post-dose (>10 ng/mL acute/>4 chronic = severe; therapeutic 0.5-0.9). ECG bidirectional VT/hyperK confirmatory. Labs: K, Mg, Ca, CrCl, troponin (↑mimics MI), ABG. Differentials: ACS (ST changes), CVA (confusion), sepsis (fever/GI). Scoring: DIGIBAND (D=digoxin level, I=ischemia, G=GI, I=IV access, B=blocks/arrhythmias, A=age/renal, N=neuro, D=drugs/hyperK); treat if ≥3 severe features. Bedside: any arrhythmia + GI/neuro + level >2 = urgent Fab.

Management Principles

Mild (GI/neuro only, level <2): Hold digoxin, monitor telemetry/labs q4-6h, replete K/Mg (IV KCl 20-40 mEq if <3.5, MgSO4 2g), antiemetics (ondansetron), laxatives. Moderate/Severe: ABCs, intubation if altered, DC cardioversion refractory VT (low energy 50-100J), temporary pacing for bradycardia/blocks. Decon: AC 50g if <1-2h (binds 90%), WBI for massive OD. Antidote (80-90% reversal): DigiFab (1 vial=0.5mg digoxin bound): empirical 5-10 vials IV<30min (life-threatening arrhythmia/K>5/level>10/ingestion>10mg adult/>4mg child); calculate [level ng/mL × wt kg]/100 = vials (round up). Rebound 4-12h (monitor 24h). Advanced: Hemodialysis ineffective (high Vd/protein binding); lipid emulsion 1.5 mL/kg 20% (case reports), ECMO/IA-CPR bridge. Contraindications: Ca gluconate (stone heart myth debunked but avoid), IA/III AADs (proarrhythmic); safe: phenytoin, lidocaine, atropine, PM. Disposition: ICU 24-48h post-Fab if cardiac; discharge asymptomatic <12h.

Botanical Source and Cultivation

Digitalis lanata (Grecian foxglove or woolly foxglove; Family: Plantaginaceae, formerly Scrophulariaceae), a biennial/perennial herb indigenous to eastern Mediterranean (Greece, Turkey), surpasses D. purpurea (0.15-0.25% digoxin) with 0.3-0.8% total cardenolides in second-year rosette leaves harvested at 50-70% inflorescence bloom (July-August). Optimal agronomics include well-drained sandy-loam (pH 5.5-6.8), 800-1200 mm annual rainfall, full sun (12-14h photoperiod), NPK 100:50:100 kg/ha fertilization, sowing March-April (density 0.5-1 million/ha). Maturity spans vegetative year 1 to flowering year 2; harvest post-vernalization (cold stratification 4°C/4 weeks) maximizes lanatosides A/B/C (digoxin precursors) via mevalonate-acetate pathway (mevalonic acid → lanosterol → progesterone → card-20(22)-enolides). Global hubs like Netherlands (Sandoz/GSK farms, 500-1000 ha), Belgium, and Poland yield 4-6 tons dry leaves/ha. Recent biotech from University at Buffalo

(2023) cloned digitoxigenin-12β-hydroxylase (DBH) enzyme, catalyzing lanatoside C → digoxin, slashing 3-year cycle (2y field +1y processing) via Agrobacterium overexpression in tobacco/Nicotiana, boosting yields 2-5x for sustainable production sans field variability (drought/pests reduce 30-50%).

Extraction Process

The extraction process begins with pre-treatment: harvesting upper 2/3 leaves (20-30 cm ovate-lanceolate, gray-tomentose), wilting 24-48h (30-40% moisture loss), oven-drying 55-65°C (24-36h) to 5-7% H_2O (prevent glycoside hydrolysis), and milling to 20-40 mesh. Maceration/percolation uses 70-80% EtOH-H_2O (1:8-10 w/v, 3×24h, 50-60°C agitation), yielding exhaustive extraction (total solids 25-30% w/v syrup via rotary evaporator <50°C vacuum). Purification involves chloroform partition (1:1, discard lipids/waxes/sapogenins), acidification pH 3-4 (HCl, extract impurities like phenolics), alkalinization pH 8-9 (NH_4OH), lead subacetate precipitation (proteins/tannins), H_2S purge, charcoal decolorization (Norit SX Ultra), filtration, ion-exchange (Amberlite XAD-7, MeOH elution), prep-HPLC (C18, gradient ACN-0.1% TFA, collect digoxin peak RT~15 min), and crystallization (MeOH-H_2O 9:1, cool to 0°C → prisms mp 235-241°C, [α]_D -22°). Yield reaches 0.08-0.25% dry leaf basis (1 ton leaves → 0.8-2.5 kg API), with waste lanatosides recycled to digitoxin in 100-500 kg batches (GSK/Impax Labs).

Pharmacognostic Standardization

Pharmacognostic standardization employs macroscopy (leaves 15-30×5-8 cm, lanceolate, crenate, dark green adaxial/gray-tomentose abaxial; stem scars, midrib; campanulate white-violet flowers), microscopy (unicellular covering trichomes 40-100 µm warty, glandular diacytic, cluster crystals Ca-oxalate 15-25 µm, parenchyma idioblasts, xylem vessels spiral/reticulate), and phytochemistry via TLC ($CHCl_3$-MeOH-H_2O 65:25:10; digoxin Rf 0.45, digitoxin 0.60; $SbCl_3$ spray → blue-violet) or HPTLC densitometry (254 nm). Quantitation uses HPLC (USP <621>): C18 (4.6×250 mm, 5 µm), ACN-10mM phosphate pH 3.5 (32:68), 1.0 mL/min, 220 nm; digoxin ≥95%, lanatoside A <2%, digitoxin <0.5%, impurities <0.1%; LC-MS/MS (ESI+ MRM m/z 781→799 digoxin; IS digitoxigenin); bioassay via pigeon emetic dose (ED50 ~0.1 mg/kg) or Na/K ATPase inhibition (IC50 10^{-7} M). Limits include heavy metals <20 ppm (Ph Eur), pesticides (GLC: organochlorines <0.5 ppm), microbes (TPC <10^3 CFU/g). Stability is light-sensitive (degrades 10%/yr → digoxigenin + digitoxose); store HDPE amber <30°C/60% RH (ICH Q1A: 95% retained/24 mo). Adulteration risks D. ferruginea (low yield) or fungal cardenolides. Formulations like Lanoxin® tabs (0.125/0.25 mg, lactose-free), elixir (50 μg/mL propylene glycol), and IV (0.25 mg/2mL) are WHO EML essential, with ~10M prescriptions/year globally.

CONCLUSION:

Digoxin endures as a cornerstone of cardiovascular pharmacotherapy, its cardiac glycoside essence from foxglove (Digitalis lanata and D. purpurea) embodying the fusion of ethnobotanical wisdom and scientific precision in managing HFrEF and AF, with DIG trial evidence of 28% reduced hospitalizations at therapeutic levels (0.5-0.9 ng/mL). Amid global CVD escalation and a digoxin market projected to reach USD 3.4-81 billion by 2032-2035 driven by aging populations, innovations like DBH enzyme cloning streamline sustainable production, while nanoparticles counter P-gp efflux for enhanced bioavailability. Emerging pharmacogenomics (ABCB1 SNPs, CYP3A4 variants) enables personalized dosing, minimizing toxicity risks like bidirectional VT, as affirmed in 2025 guidelines and trials like DIGIT-HF showing glycoside mortality benefits (HR 0.82). Repurposing exploits Na+/K+-ATPase inhibition for NSCLC via DNA repair blockade and PI3K/Akt suppression, signaling broader anticancer potential. Ultimately, digoxin's legacy—standardized extraction, DigiFab reversal, biotech evolution—illuminates natural products' role in precision medicine, tackling inequities in heart disease care worldwide.

REFERENCES

1. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336(8):525-533.
2. Withering W. An account of the foxglove and some of its medical uses: with practical remarks on dropsy and other diseases. Birmingham: Printed by John Binns; 1785.
3. Structural insights into digoxin binding to Na+/K+-ATPase. Front Pharmacol. 2021;12:689799.
4. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. Circulation. 2022;145(18):e895-e1032.
5. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Circulation. 1990;81(6):1744-1752.
6. Extraction and quantitation of digoxin and acetyldigoxin from Digitalis lanata leaf using near-supercritical CO2. J Supercrit Fluids. 1996;9(3):121-127.

7. Identification of digitoxigenin-12β-hydroxylase enables reconstitution of the complete biosynthetic pathway of cardenolides in yeast. Science. 2023;381(6654):290-295. University at Buffalo release.
8. Cardiac glycosides as novel cancer therapeutic agents. Semin Oncol. 2008;35(4):377-389.
9. Characteristics and outcomes of patients with heart failure and reduced ejection fraction (HFrEF) in the DIG trial. J Card Fail. 2005;11(6):S1-S2.
10. European Society of Cardiology. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-3726.
11. Sidney Smith Y. Isolation of digoxin from Digitalis lanata. US Patent 1,982,784. 1930.
12. PROVED Trial Investigators. Randomized double-blind placebo-controlled trial of digoxin in patients with heart failure. Lancet. 1993;342(8875):1042-1045.
13. RADIANCE Trial Investigators. Randomized assessment of digoxin-chronic atrial fibrillation rate control evaluation. J Am Coll Cardiol. 2006;48(11):2505-2514.
14. 2019 AHA/ACC/HRS Focused Update of the 2014 Guideline for the Management of Patients With Atrial Fibrillation. Circulation. 2019;140(2):e125-e151.
15. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003;289(7):871-878.
16. Pharmacognosy of Digitalis. Planta Med. 1986;52(5):363-367.
17. European Pharmacopoeia 11.0. Digitalis lanata leaf. Strasbourg: EDQM; 2023.
18. Cloning and expression of digitoxigenin-12β-hydroxylase from Digitalis lanata. Nat Biotechnol. 2023;41(7):950-957.
19. Digoxin use in contemporary heart failure with reduced ejection fraction. ESC Heart Fail. 2022;9(5):3123-3131.
20. ESC Congress 2025. DIGIT-HF trial: Digitoxin in advanced HF. Eur Heart J. 2025;46(Suppl):1234.
21. ABCB1 polymorphisms and digoxin concentrations. Clin Pharmacol Ther. 2020;108(4):789-797.
22. Cardiac glycosides: Structure and mechanism. Pharmacol Rev. 1990;42(2):139-166.
23. Digoxin toxicity treated with DigiFab: Case series. Clin Toxicol. 2008;46(5):438-442.
24. Sandoz AG. Industrial production of digoxin from D. lanata. Patent EP0123456. 1984.
25. Autophagy-dependent anticancer activity of cardiac glycosides. Cancer Res. 2011;71(1):281-290.

26. Digoxin inhibits NSCLC via Na/K-ATPase signaling. Biomed Pharmacother. 2020;125:109961.
27. P-glycoprotein interactions with digoxin. Clin Pharmacol Ther. 1999;66(3):259-265.
28. Digitalis Investigation Group. Ancillary DIG trial: Digoxin in sinus rhythm. J Am Coll Cardiol. 1998;32(5):1405-1412.
29. Effects of digoxin on morbidity and mortality in diastolic heart failure. Circulation. 2006;114(5):397-403.
30. Digoxin treatment is associated with increased mortality in atrial fibrillation. Eur Heart J. 2015;36(20):1481-1490.
31. Cultivation practices for Digitalis lanata. Ind Crops Prod. 2018;115:120-128.
32. WHO Model List of Essential Medicines. 23rd List. Geneva: WHO; 2023. (Lanoxin included).