J. Sci. Innov. Nat. Earth: Vol. 5, Issue 1, 2025, Page 23-28 ISSN (Online) 2583-2093

OPEN ACCESS

Journal of Science Innovations and Nature of Earth

Journal homepage : https://jsiane.com/index.php/files/index

International, Double-Blind, Quarterly, Peer-Reviewed, Refereed Journal, Edited and Open Access Research Journal

Overview Study on Characterisation Chemistry and Pharmacology of Digitalis Glycosides

Ashutosh Pathak[*1, 2], Priya Awasthi[4], Umair Ahmad[5], Vinit Kumar[6], Neeraj Bharti[4], Pavan Kumar[3], Salman Ahmad Khan[1]

[1]Department of Pharmaceutical Chemistry, Institute of Pharmacy, Dr. Shakuntala Misra National Rehabilitation University, Mohan Rd, Sarosa Bharosa, Lucknow, Uttar Pradesh, India – 226017

[2]Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences (SHUATS), Prayagraj, Uttar Pradesh - 211007, India

[3]Institute of Engineering and Technology, Dr. Shakuntala Misra National Rehabilitation University, Mohan Rd, Sarosa Bharosa, Lucknow, Uttar Pradesh, India – 226017.

[4]Department of Pharmaceutical Chemistry, Maharana Pratap School of Pharmacy, Mohanlal Ganj Lucknow, Uttar Pradesh, India-226301

[5]Institute of Pharmacy, Department of Pharmaceutical Chemistry, integral University, Kursi Rd, Dashauli, Uttar Pradesh, India- 226026

[6]Institute of Pharmacy, Department of Pharmacology, Saroja school of pharmacy, Ahemamau, Lucknow, Uttar Pradesh, India – 226002

Corresponding Author E-mail: rrscopashu1986@gmail.com, pkchtp8@gmail.com

DOI: https://doi.org/10.59436/jsiane.302.2583-2093

Abstract

Medicinal plants influence human health worldwide and are an integral part of the ecology and environment. Pharmacologically, they have been used to address a number of different ailments in the past. The healing value of plants is attributed to the amount of active chemicals present in their different portions. This review aims to present a current assessment of cardiac glycosides present in African medicinal plants as potentially beneficial treatments. Google, Google Scholar, PubMed, Medline, Research Gate, Web of Sciences, ScienceDirect, and Sci Finder were among the online resources used in the literature review. The keywords "natural goods," "pharmacology," "isolated compounds," "cardiac glycosides," "African medicinal plants," and "bioactivity" were employed. Cardiac glycosides have been identified since ancient times and isolated from plants and animals. By strengthening myocardial contractions and reducing their frequency, cardiac glycosides have been employed as drugs to treat heart disorders. As A growing amount of research has. Demonstrated, the biological consequences of these drugs go beyond their capacity to inhibit sodium-potassium pump function. Endogenous and external cardiac glycosides can affect the immune system, bodily défense, carcinogenesis, and hormone regulation, among other processes regulated by these transcription factors, by their interaction with nuclear receptors. Digoxin's proven efficacy, cost, and global accessibility ensure its continued relevance even in the face of newer pharmacological drugs. African medicinal plants have produced several cardiac glycosides with well-established pharmacological characteristics, such as neurotoxic, antiviral, enzyme-inhibitory, cytotoxic, and anti-inflammatory effects. Additionally, they can be thought of as starting Combinatorial chemistry structures, which produces fresh molecules with the intended features, including medications. Particularly common cardiac glycosides are found in the Asclepiadaceae and Apocynaceae families.

Keywords: *Digitalis purpurea*, digoxin, lanatoside C, Plantaginaceae, lucibufagins, ventricular response, Datura

Received 06.01.2025 **Revised 06.02.2025** **Accepted 01.03.2025**

Introduction

Certain plants, invertebrates, and vertebrates create a class of secondary metabolites known as cardiac glycosides. *Digitalis purpurea* (digitoxin), *Digitalis lanata* (digoxin, lanatoside C) (Batterman, *et al*, 1947 and Hollman, *et al*, 1996), Nerium oleander (oleandrin) (Yeau , *et al*, 1965 and Blum, *et al*, 1987), and Antiaris are some of the most prevalent plants that produce cardiac glycosides. *Convallaria majalis* (which produces convallatoxin) and toxicaria (which produces antiarosides) (Li X.S., *et al*, 2014), and *Convallaria majalis* (producing convallatoxin) (Lautenbacher *et al*, 2014). Toads belonging to the Rhinella, Bufo, and Rhaebo genera (bufalin, marinebufagin, resibufagin, and telocinobufagin), fireflies Lampyridae (lucibufagins), and snakes Rhabdophis tigrinus (gamabufotalin) are among the animals that produce cardiac glycosides (Steyn *et al*, 1998, Eisner *et al*, 1978 and Hutchinson *et al*, 1978).

Domain	Eukaryotes
Kingdom	Plantae
Genus	Digitalis
Order	Lamiales
Family	Plantaginaceae
English name	Digitalis
Scientific name	*Digitalis purpurea*
Common name	Foxglove
Urdu name	Datura

Botanical description:

There are two varieties of this herb: biennial and perennial. Its height ranges from one to two meters. Fruit and Bloom: The inside of the carmine-red blossoms is rimmed with white. The racemes of flowers hang in lengthy strands. Five short-tipped sepals are free. About 4 cm long, the campanulate, bilabiate flower has an oval apex on the lower lip and an obtuse top lip. The bloom has a white pawn within and is glabrous on the outside. Along with one superior ovary, there are two long and two short stamens. The fruit is an oblong, glandular, villous capsule with two valves that is attached to the taproot of the branching plant. Most leaves are crenate, with just the highest having entire edges. The rough, hairy, oblong to oval-lanceolate, usually dark green leaves of the foxglove grow from 10 to 25 cm in length and make up the basal rosette. (Bricknell *et al*, 2003)

Habitat:

The foxglove has become native to a number of places, including North America, Australia, and New Zealand, as a result of its appeal as a garden ornament (Willis, *et al*, 2000). In Hungary, Austria, England, Germany, and Japan, it is grown commercially as a medicinal plant. It is cultivated in India's Nilgiri, Kashmir, and Darjeeling regions. The foxglove's natural habitat is as a wildflower, not as a decorative plant for a garden. Throughout its natural range in Europe and Great Britain, it is widely distributed in unmanaged habitats and disturbed open ground; New Zealand is part of its naturalized ranges. These environments include roadsides, track sides, stony river beds, scrub and woodland borders, and poor pastures. Among the most prevalent New Zealand's naturalized species wetter regions is the foxglove, which is widely distributed along the South Island's West Coast and can reach elevations of up to 1000 meters above sea level (Webb *et al*, 1988 and Cameron *et al*, 1989).

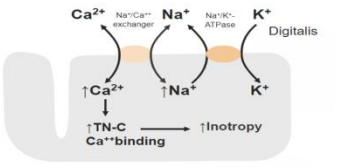
Background:

A class of substances known as cardiac glycosides, digitalis glycosides, and digitalis are derivatives of steroids that can cause different electrophysiological reactions and somewhat increase myocardial contractility. Digoxin, an extract from the leaf of the *Digitalis lanata* plant, and digoxin, an extract from the *Digitalis purpurea* plant, are the most often utilized substances. Both plants belong to the family of foxgloves. A lactone ring, many sugars connected to the nucleus' carbon 3, and a steroid nucleus make up a cardiac glycoside. Aglycones are made up of the steroid nucleus and the lactone ring. One of the main elements influencing a medication's half-life is the quantity of sugar moieties it contains, however other factors also come into play. For inotropic action to occur, the lactone ring is required. (Gordon *et al*, 2008) Digitalis glycosides allosterically inhibit the protein cation pump Na+-, K+-ATPase, which uses the energy from ATP hydrolysis to actively transport potassium ions inside cells and sodium ions outside (when K+: Na+ is 2:3). The small amount of enzyme inhibition brought on by the therapeutic amounts of digitalis chemicals (about 30%) is

enough to momentarily increase the Na+ level in the cell. The sarcoplasmic reticulum releases more calcium that can bind to troponin-C and increase heart muscle contractility when the Na+/Ca2+ exchanger is blocked, which raises the intracellular Ca2+ concentration (Bartnik., *et al*, 2017). It has been demonstrated that heart failure with reduced ejection fraction (EF), or CHF with reduced EF (HFrEF), provides benefits, particularly when taking into account the total impact of lower hospitalizations, morbidity, and mortality. Digoxin is typically recommended for atrial fibrillation (AF) with a rapid ventricular response when thinking about a rate control plan. Since all other rate-control drugs exacerbate hypotension, digoxin offers the best support of any drug for AF rate control in the presence of marginal blood pressure. In conclusion, digoxin seems to work best these days for rate control in conditions like HFrEF and AF with rapid ventricular response, particularly when hypotension is present (Deshmane, *et al*, 2022).

Mechanism of Action:

Digoxin's combination inotropic-bradycardic action sets it apart from all other sympathomimetic inotropes that induce tachycardia. Its main mode of action is blocking the sodium pump, the intrinsic membrane protein Na+-K+ ATPase, which facilitates calcium input through a sodium-calcium exchange mechanism. The drug's inotropic and electrophysiological effects are the outcome of this influence. Atrioventricular (AV) nodal inhibition and sinus slowness are further effects of digoxin's parasympathetic activation. Digoxin causes diuresis and lowers serum aldosterone, norepinephrine, and plasma renin activity in heart failure patients. This inhibition causes intracellular sodium to accumulate and the sodium-calcium exchanger's function to decrease. Calcium levels within cells rise as a result, increasing cardiac contractility and promoting more calcium binding to troponin C. Digoxin also acts acting as a negative chronotropic, lowering heart rate. Because of its restricted therapeutic window, serum digoxin levels need to be continuously controlled to minimize hazardous risk (Webb *et al*, 1988 and Cameron *et al*, 1989).



Drug kinetics:

Digoxin is a cardiac glycoside medication that is frequently used to treat various heart conditions, including congestive heart failure, atrial fibrillation, and certain cardiac arrhythmias. Blocking sodium-potassium adenosine triphosphatase (Na+/K+ ATPase), which is mostly present in the heart, is its primary method of action. This inhibition raises blood pressure, myocardial contractility, and stroke volume while lowering heart rate. Digoxin has a narrow therapeutic range, and symptoms such as arrhythmias, nausea, vomiting, and visual anomalies may be signs of toxicity. When taken orally, digoxin is not fully absorbed; a large amount is eliminated by the kidneys, leading to 70–85% excretion through urine. Digoxin oral dosages typically have a 50–90% bioavailability, while gelatinized digoxin capsules have been shown to have a 100% bioavailability. For maintenance therapy, the usual range is 0.125–0.25 mg/day, while for loading dosages, it is 0.01–0.02 mg/kg. Digoxin is still an essential component of the traditional treatment for heart failure, even if its use has declined as other medicines have become available. Digoxin has been used for more than 200 years. Conflicting current research on Digoxin's effects on morbidity and mortality requires more research and a more precise evaluation of its possible future significance in light of fresh information. (Currie, *et al*, 2011and David, *et al*, 2024). Digoxin is absorbed by around 70 % of the gastrointestinal tract following oral therapy (Hausner *et al*, 2017). It is estimated that Serum albumin binds 25% of digoxin. Digoxin has a high distribution volume because it binds to muscle tissue extensively, basically leaving fat tissue unattached. Digoxin crosses the placental barrier and the cerebrospinal fluid before entering the mother's milk (Saunders, N.R., *et al*, 2019). Digoxin has an elimination half-life of 36 to 48 hours in the case of normal renal function, and its excretion by the kidneys is exponential. In premature newborns, the elimination half-life could range from 61 to 170 hours. According to reports, gelatinized digoxin capsules have a 100% bioavailability, whereas oral dosages typically have a 50–90% bioavailability. Loading doses usually lie within the range of 70% that the gastrointestinal system can absorb. 4–5 half-life (7–10 days) later steady-state plateau concentrations are reached in subjects with normal renal function who began taking medication at maintenance dosages. Patients suffering from renal insufficiency need lower loading and maintenance dosages of digoxin since their volume of distribution is reduced. Digoxin oral dosages usually have a 50–90% bioavailability, although gelatinized digoxin capsules have been found to have a 100% bioavailability. When loading dosages are taken orally, the gastrointestinal tract typically absorbs digoxin in about 70% of cases (Hausner *et al*, 2017). Digoxin is thought to be 25% bound to serum albumin. Due to its significant binding to muscle tissue, digoxin essentially leaves fat tissue unattached, resulting in a high distribution volume. Digoxin enters the mother's milk after passing through the placental barrier and the cerebrospinal fluid (Saunders *et al*, 2019). Digoxin has an elimination half-life of 36 to 48 hours in the case of normal renal function and is eliminated by the kidneys exponentially. In premature newborns, the elimination half-life could range from 61 to 170 hours. After 4 to 5 half-lives (7–10 days), steady-state plateau concentrations are reached in individuals with healthy kidneys who began taking medication at maintenance dosages. Patients suffering from renal insufficiency need lower loading and maintenance dosages of digoxin since their volume of distribution is reduced.

Pharmacodynamics:

The proximal portion of the small intestine absorbs between 70 and 80 percent of the oral digoxin dosage. Twenty to thirty percent bind to serum albumin. The large volume of dispersion suggests that digoxin is extensively dispersed throughout the tissues. Digoxin's absorption in the heart after ingestion is closely related to its pharmacodynamic effects. Both the cardiac and serum concentrations of digoxin are associated with its harmful effects. Due to its limited therapeutic window, digoxin's pharmacokinetics and pharmacodynamics can be greatly impacted by variables such body weight, serum albumin concentration, renal function, and medication interactions. Digoxin is still a useful treatment for atrial fibrillation and heart failure, despite being one of the oldest drugs in cardiology. However, because of the possibility of toxicity, especially when supratherapeutic doses or chronic overexposure are involved, its use requires close monitoring. Digoxin is crucial for the treatment of certain cardiac conditions, as evidenced by its notable pharmacodynamic effects on the cardiovascular system. (Chen *et al*, 2012). In addition to its direct actions on the smooth muscle vascular system and myocardium, it also has indirect anti-arrhythmic effects (lowering conductivity AV node), negative chronotropic effects (slowing heart rate), and positive isotropic effects (raising myocardial contraction force) (Komatsu *et al*, 2015). Digoxin is a positive inotropic, meaning it increases the force of the heart's contraction by blocking the sodium-potassium adenosine triphosphatase (Na+/K+-ATPase) pump. This inhibition causes intracellular sodium to grow along with intracellular calcium. Increased calcium causes the heart to contract more forcefully.

Digoxin reduces electrical conduction through the atrioventricular (AV) node by activating the parasympathetic nervous system. This reduces the heart rate and decreases the ventricular response.

-Reduced sympathetic nerve activity: Digoxin reduces sympathetic nerve activity, renin angiotensin activity, and circulating catecholamines.

-Increased stroke volume: Digoxin increases both the volume of the stroke and the cardiac output each beat.

-Decreased conduction velocity: Digoxin slows down the rate at which data passes through the AV node.

Chemical constituents:

The cardiac glycosides are made up of one or more sugar molecules plus an aglycone, also known as genin. For example, three molecules of digitoxose are joined to an aglycone known as digoxigenin to form digoxin, the cardiac glycoside most frequently utilized in clinical settings in the United States. Aglycones, which comprised of an unstructured lactone ring and a steroid, have the same medicinal and deleterious characteristics as glycosides. Compared to cardiotonic medications, they frequently have shorter half-lives and lower efficacy. (Gheorghiade *et al*, 2004) According to the conventional structure-activity relationship, inotropic activity was only observed in derivatives that had a 17beta unsaturated lactone ring in place of the 14beta-hydroxysteroids and that also had the cis/trans/cis configurations at the ring junction, which are the stereochemical characteristics of digitalis steroids. The transfusion between the C and D rings of corticosteroids, do not produce digitalis-like effects. Later research, however, revealed that digoxin is not the only more potent A-B trans molecule; There is no need for cis fusion at the C-D junction, and the lactone ring's double bond and the C-14 hydroxyl group are not required (prednisolone3,20-bisguanylhydrazone). When a C-14 hydroxyl group is replaced due to hydrogen, lactone ring saturation in order or modification, the inotropic effect is no longer effective but its potency is significantly reduced (Heidenreich *et al*, 2022). Three of the four prominent glucosides found in digitalis are coronary stimulants. The crystalline molecule digitalin is insoluble in water, Digitoxin, this is the case extremely toxic and cumulative, and despite being amorphous, digitalein degrades rapidly in water, are the most powerful of these. They can be administered subcutaneously in doses as small as a grain. Digitonin depresses the heart that is same as saponin, the primary component of Senega root, and has no physiological activity in common with Digitalis. Sugar, flour, gum, fatty substances, and volatile oil are additional constituents. The amount and type of active substances are affected by soil and season: One hundred parts of dehydrated leaves provide around 1.25 parts of digitalin, which can be found in the wild at greater quantities than in plants that are domesticated. Its action on circulation is the drug's most crucial characteristic. Each kind of muscle tissue is more active as consequence, but the heart and arterioles are undergoing greater activity.

Often referred to as digitalis or glycosides of digitalis, cardiac glycosides—specifically, Digitoxin and Digitoxin—in the past, mainstay of heart disease therapy for almost 200 years. However, their clinical utility has been greatly diminished since the discovery of β-adrenergic blockers, angiotensin receptor blockers, and angiotensin-converting inhibiting enzymes. Heart glycosides have a low medicinal index. Through an assortment, they have numerous cardiovascular effects. (Negi *et al*, 2012, Whalen *et al*, 2015 and Jorgensen *et al*, 2003). The effects of Digitalis should be closely monitored in all of its forms, and it should be used cautiously when taken for an extended length of time because it has the potential to build up in the body and show up all at once through its toxic action, which is manifested by an irregular pulse, low blood pressure and the onset of unease in the gastrointestinal tract. Likewise frequent use of Digitalis weakens the heart by becoming more active, which causes the organ to enlarge. Digitalis, injected via a hypodermic injection, is a great remedy for aconite poisoning. Prior to and following flowering, the levels of manganese (Mn), cobalt (Co), nickel (Ni), copper (Cu), arsenic (As), boron (B), chromium (Cr), and lead (Pb) in different parts of vegetation of Digitalis were measured. The stage after blossoming had larger concentrations of the majority of the minerals than the pre-flowering stage (Lee *et al*, 2006).

The medicinally used leaves of wild species comprise a minimum of 30 distinct glycosides, ranging in total concentration from 0.1% to 0.6%. Glycoside B makes up most of these glycosides, the precursor to gitoxin, and glycoside A from purpura, yielding digitoxin. The C-14 hydroxyl group's solitary apparent purpose is to align the lactone ring with the steroid nucleus at the proper angle. Besides the binding sites corresponding to the unsaturated lactone ring at position C-1 7, the receptor also has a sugar affixed at position C-3. Consequently, these structures alter the compound's affinity but not its effectiveness for the beneficial inotropic effect. Unsurprisingly, there are no stringent structural constraints because the cardiac glycoside shares pharmacological characteristics with various chemical structures, including cassaine and prednisolone-3,20-bisguanylhydrazone. The quantity and location of hydroxyl groups vary among the different glycosides and aglycones. The hydroxyl groups have a crucial role in a compound's duration of the action, interactions with proteins, lipid solubility, and biologic transformation. Despite what many people believe, digoxigenin or the molecules that bind to it do not make the substance more soluble in water or less soluble in lipids. (Guntert *et al*, 1981)

Toxicology

The plant is poisonous in all sections. Grazing causes animal poisoning. Children have become ill after sucking the flower petals or consuming the seeds or leaf fragments. Those who drank tea brewed from digitalis, which was misidentified as comfrey, have been known to die. However, its emetic qualities can cause vomiting, which limits systemic absorption, and its bitter taste frequently discourages consumption. Intentional utilization with suicidal intent is also linked to digitalis poisoning. (Jowett *et al*, 2002, Lacassie *et al*, 2000 and Lin *et al*, 2010). In severe cases, stupor, confusion, seizures, and death could happen along with vision problems, compressed pupils, light-headedness, excessive urination, tiredness, weakness of the muscles, nausea, a strong but delayed pulse, tremors, vomiting, and nausea are manifestations of plant or refined chemical intoxication. Visual halos, yellow-green eyesight, and digestive issues are signs of chronic digitalis intoxication. (Dick *et al*, 1991, Hauptman *et al*, 1999 and, Morton *et al*, 1977)

Preparation:

There are wide variations in the potency and composition of foxglove medications available on the market. Digitalis leaves are provided as ground-up tablets. The most popular mixture, the pharmacopoeial tincture, is administered in 5.15 microgram doses, whereas the infusion is administered at a very tiny quantity of two to four drachms. For other infusions, the dosage is one ounce or more. The poison is digitized, and there is an adequate quantity of Digitalin in the tincture.

Cultivation and Collection:

Digitalis seeds are sown in a sand mixture due to they are small. In both years, leaflets are gathered, but they are collected after two-thirds of the blooms have bloomed. The seedling is then transferred to the field. Since the most cardioactive glycosides are believed to be present in the early afternoon, this is when the leaves are usually plucked. The leaves are immediately dried below 60 C after collection and then put in sealed containers. The dried leaves' moisture level shouldn't be higher than 5% because this promotes the breakdown of cardiac glycosides, which lowers heart activity.

Seed Gathering:

When seeds are ready, they must be collected. Instead of being pale, white, or other colours, true medicinal blooms must be pure, deep pink, magenta or speckled on the outside. It is believed that at least two tons of Foxglove foliage can be grown in one acre of suitable soil, yielding almost half a ton of dried leaves. To produce the green rosette, seeds should be sown in the late spring while they are being grown. The seeds should be combined with fine sand to guarantee even dissemination because they are so tiny and light. They should have a light layer of soil applied. Despite the germination of the seeds is uncertain, the seedlings can be securely and easily shipped in humid conditions and should be spaced 6 to 9 inches apart. Seeds need to be picked as soon as they are ready. Instead of being pale, white, or other colours, true medicinal blooms must be pure, deep pink, or magenta on the outside. It has been suggested that at least two tons of Foxglove foliage may be grown in one acre of suitable soil, yielding almost half a ton of dried leaves. (Bricknell\ *et al*, 2003)

Isolation and Purification of Digoxin:

Digoxin, a cardiac glycoside used to treat heart issues, originated by Dr. Sydney Smith in 1930 from the foxglove plant *Digitalis lanata*. Digoxin is among the substances produced by the isolation method, which involves removing the fuzzy foxglove's glycosides. Digoxin is then purified by dissolving its glycosidic linkages in the body, which results in the formation of digoxin and sugars. Rather than being synthesized in a lab, digoxin's herbal origins are what make its discovery historically significant. William withering, a British In 1775, a doctor discovered that the foxglove plant has external therapeutic benefits for treating conditions including dropsy (oedema). This discovery has led to the widespread usage of digitalis in medicine. Pure digoxin for use in medicine is still produced from the foxglove plant using a modern process that extracts digitalis from dried foxglove leaves (Lyon, *et al*, 2016). Since its extraction and purification from *Digitalis lanata*, digoxin has been used extensively to treat a range of cardiac conditions during the past century. This historical excursion highlights the continued significance of natural sources in the development of new drugs.

Extracting the digitalis glycosides from *Digitalis purpurea* and *Digitalis lanata* requires a multi-step procedure. Natural extracts are first made using solvents such as methanol, alcohol, chloroform, or ether. Continuous solvent extraction is achieved by Soxhlet extraction following the removal of volatile pollutants by subsequent steam distillation. Purification Purification methods like high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), and column chromatography are used to crystallize digoxin, digitoxin, digitalin, and gitoxin. Additional purification procedures include desalting, decolorization, and defatting. Digitoxin's yield and purification range from 0.5-1.5% and 95-99%, respectively, while its yield is 0.2-0.5% with 90-95% purity. Sophisticated methods including Supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), and pressurized liquid extraction (PLE) increase efficiency and selectivity. The intricacy of glycoside combinations, the unpredictable nature of plant materials, and problems with scaling for industrial production, however, continue to provide challenges. Plant sources include ***Digitalis purpurea*** and ***Digitalis lanata*****.**

Pharmacological studies:

Cardiovascular activity and mechanism:

We looked into isolated cardiac arrhythmias in rabbits, urine excretion in rats, and the emetic effects of a glycoside produced from *Digitalis purpurea* in pigeons. At 20 and 40 mg/ml, the methanolic extract raised the contraction force of the auricle in a dose-dependent way. At dosages of 15 and 30 mg/kg, a modest diuretic and natriuretic action is observed. With an active dose range of 0.5–4 mg/kg, it was shown that the emesis time decreased in a dose-dependent way within 10 minutes of injection. Digitalis glycosides not only compete with potassium for binding to potassium ATPase (Na+/K+_ATpase), but they also stop potassium from doing so (Navarro *et al*, 2000).

Hepatoprotective activity:

Albino rats exposed to CCl4-induced hepatotoxicity were used to evaluate the hepatoprotective effectiveness of *Digitalis purpurea* methanolic extract. Hepatotoxicity was evaluated by measuring serum concentrations of alanine aminotransferase (SGPT), aminotransferase with aspartate (SGOT), alkaline phosphatase (ALP), and total bilirubin. Serum values of SGOT, SGPT, ALP, and total bilirubin were elevated, indicating significant liver injury in rats given CCl4. The harmful effect of CCl4 on the aforementioned serum parameters is inhibited by the administration of silymarin and *Digitalis purpurea* extract in both preventive and curative models (Rabadia *et al*, 2014).

Atrial Fibrillation Management:

Digoxin is advised as a cardiac glycoside for a number of ailments, such as heart failure in individuals with persistent atrial fibrillation while maintaining ventricular rate control. Digoxin is a positive inotropic and negative chronotropic medication that helps treat atrial fibrillation by lowering heart rate and boosting cardiac contractility. Despite being used for many years to treat heart failure, recent research has not definitively demonstrated that it reduces mortality rates. Digoxin, however, has demonstrated potential in lowering hospitalizations brought on by worsening heart failure. When choosing to use digoxin to treat heart failure or atrial fibrillation, one should take into account the risks and features of each patient (Pervaiz *et al*, 2006 Virgadamo *et al*, 2015 and David *et al*, 2024).

Determining whether digoxin medication is appropriate requires a thorough assessment of the clinical state and therapy of the patient.

Other Therapeutic Uses:

Digoxin is primarily used to treat cardiac disorders like atrial fibrillation, congestive heart failure, and certain cardiac arrhythmias. Usually, it is administered in combination with other drugs like ACE inhibitors and diuretics. However, digoxin intoxication can cause symptoms like nausea, vomiting, and vision impairment because of its limited therapeutic range. anomalies, and irregular heartbeats. Digoxin is still often used to treat heart failure even if more contemporary therapy options have become available. Interestingly, the most recent guidelines from the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of America (HFSA) advocate digoxin as a medicine for some heart failure patients.

Abortion:

Potential of Digoxin as an abortifacient was sparked by early research that indicated it might cause uterine contractions. However, limited use in this setting was caused by worries about its efficacy and safety (Gheorghiade *et al*, 2004). The medical community chose alternate methods with more proven efficacy and safety profiles as a result of the unclear results, which made it cautiously applied for pregnancy termination.

Hypertension: Digoxin's ability to reduce blood pressure has been studied, yet its long-term effectiveness in treating hypertension is questionable. Because of conflicting data on its long-term efficacy and worries about its safety profile, as a first-line treatment for hypertension, it is not advised.

Cardio protection:

Acute myocardial infarction and surgery have been studied to determine whether digoxin has cardioprotective effects. However, it is not yet understood how digoxin will impact morbidity and death overall in these settings. Despite early excitement over its cardioprotective traits digoxin's ability to improve clinical results following surgery or a MI condition has not yet been shown.

Angina pectoris: Research has shown that digoxin can lessen coronary artery disease-related chest discomfort. But it is not widely used, and there is doubt about how well it works to treat angina pectoris. The lack of solid evidence for digoxin's efficacy and the accessibility of more potent treatment alternatives like beta-blockers as well as nitrates have limited it to a supportive role in the management of angina.

Adverse medication reactions: Digitalis formulations' pharmacokinetics may be changed directly by taking medications at the same time, or pharmacodynamic interactions may change their effect on the heart indirectly. The amount of distribution of digoxin of digoxin and renal and non-renal excretion are both reduced by quinidine. Quinidine's strong Digoxin transport across epithelial cell membranes, particularly in the kidney, has been demonstrated to be limited by affinity for P-glycoprotein, an ATP-dependent efflux pump generated by the mdr1a gene. Digoxin dosages should be adjusted since amiodarone medicine increases the steady-state concentration of digoxin lowered via half for maintenance. It will prove crucial for keep a careful eye out for interactions between newly approved treatments and cardiac glycosides. Pharmacodynamic interactions include the use of a concurrently delivered diuretic treatment. Through volume depletion, which lowers the glomerular filtration rate, and electrolyte imbalances such as hypokalemia, hypomagnesemia, and hypercalcemia, these treatments may increase the risk of Digitalis toxicity. Using different antiarrhythmic medications at the same time may also increase the chance of arrhythmic events, though this can vary from patient to patient. (Petrovna *et al*, 2023)

Historical Uses: Digitalis species were formerly used to cure infections, comes to a boil ulcers, headaches, and paralysis. Digitalis species were applied externally to treat ulcers and granule wounds that did not heal well. Digoxin, a life-saving assistance heart medication, is extracted from Digitalis species following William Withering's study. Among its many conventional Digitalis has long been used as a heart failure cure.

Principal Species: Foxglove is a common ornamental for gardens, and many cultivars and hybrids have been produced in a range of colours. D. grandiflora, also known as golden foxglove; D. lutea, sometimes known as straw foxglove; D. ferrugineol, also known as rusty foxglove; and D. parviflora or chocolate foxglove, or small-flowered foxglove, are supplementary garden species. Widespread production of both ordinary and Grecian foxglove (D. lanata) is used to produce the heart-stimulating therapeutic digitalis. The medicine is made from the leaves that have been desiccate.

Obstacles and Restrictions:

Limited Therapeutic Index: Digoxin is well known for having a limited therapeutic index, meaning that even little variations in plasma concentration can quickly lead to hazardous or subtherapeutic levels (Currie *et al*, 2011). Digoxin has a broadly recognized therapeutic range of 0.8 to 2.0 ng/mL, with doses beyond 2.4 ng/mL considered hazardous. However, inconsistencies in the therapeutic thresholds used by different laboratories have led to debates about whether digoxin's reference ranges ought to be updated (Gona *et al*, 2023). Vigilant monitoring of digoxin levels is essential due to its limited therapeutic window; regular evaluations are advised to maintain concentrations within the ideal range for safety as well as effectiveness (Currie *et al*, 2011).

Individual variety in Response: One major obstacle in clinical practice is the variety in individual responses to digoxin. The limited therapeutic index of digoxin and significant Systemic fluctuation make it difficult to achieve the right dosage, which calls for careful tracking of the levels of digoxin in the serum (Abdel *et al*, 2020). Digoxin dosage guidelines that are unique to patient subgroups, such as Japanese Atrial fibrillation and heart failure patients have been developed in large part thanks to population pharmacokinetic analyses (Hirai *et al*, 2022). Nevertheless, despite these initiatives, digoxin response is still influenced by individual characteristics such as age, kidney functioning, and concurrent medication interactions, necessitating careful monitoring and customized doses (Dasgupta *et al*, 2016).

Emerging Alternatives and Competition: Newer treatments that claim lower death rates for heart failure patients have put Digoxin, a drug with a long history of treating heart failure, up against competition. Digoxin use has decreased as a result of recent research that has not conclusively demonstrated the mortality benefits of digoxin in comparison to these cutting-edge therapies. Digoxin may still be effective in treating heart failure, though, based on a closer examination of its pharmacological effects and the results of current trials. Some studies indicate potential advantages such as reducing hospital admissions without affecting overall mortality rates, despite digoxin's declining use. Additionally, customized dosage plans and research on digoxin's impact on vascular smooth muscle cells and neointima formation reveal probable applications for the drug in specific populations of patients or ailments (Pervaiz *et al*, 2006).

Recent Developments:

Digoxin, a drug that has long been used to treat cardiac problems, has recently been the subject of debate over its safety and effectiveness. Digoxin therapy has been shown to offer both advantages and disadvantages in recent research; some studies have suggested advantages for particular patient populations, while others have raised concerns about possible hazards. Understanding the market dynamics, important drivers, and new prospects are the main goals of current research trends and studies on digoxin. Safety issues have been brought up by recent studies by linking Digoxin use is linked to heart failure and higher mortality hospitalisation. However, a global analysis of the digoxin market offers information about trends that are approved by leading producers, advancements in technology and the competitive environment. Controlled-release formulations, targeted drug delivery systems, and nanoparticles are all current research fields that possess the potential to drastically change medicine administration, optimize patient outcomes, and lessen adverse effects (Chang *et al*, 2023).

Outlooks for the future:

Research Patterns and Current Investigations: Digoxin, a drug that has long been used to treat cardiac problems, has recently been the subject of debate over its safety and effectiveness. Both beneficial and detrimental attributes of digoxin medication have been discussed in recent research; some have raised concerns about potential hazards, while others have recommended benefits to specific patient categories (Ziff, *et al*, 2016). Understanding digoxin's market dynamics, major drivers, and new prospects is the main goal of current research trends and studies. Assessment of the global digoxin market offers insights into competitive environments, technological advancements, and trends adopted by significant producers (Lacassie *et al*, 2000). Digoxin's use in modern practice has decreased despite its historical significance because safer and more effective heart failure treatments are now available (Sapna *et al*, 2023).

Prospective New Uses: Digoxin's prospects cover both its possible advantages and disadvantages as it works through its place in contemporary medicine. Digoxin was believed to be useful historically, but current investigation indicates it may affect patients' autonomic function (Ziff *et al*, 2016). Recent research, however, has sparked worries about safety, linking digoxin use to higher rates of death and hospitalization for heart failure (Chang *et al*, 2023). The entire global digoxin sector is being examined for trends and prospects between 2023 and 2030. Leading companies in this industry, including Merck, Pfizer, and Cipla, place a high value on cutting-edge technologies and environmentally friendly operations. Factors like Standards for cleanliness transcending or dropping below 98%, as well as apps such as tablets and injectable goods are taken into account when segmenting the market.

Technological Advancements in Drug Delivery:

Developments in the Technology of Drug Delivery Digoxin has a long history of medicinal usage as a cardiac glycoside to treat heart failure and certain arrhythmias. However, its use as a first-line treatment has decreased as a result of recent research, such as the Digitalis Investigation Group (DIG) study, casting doubt on its efficacy and dependability (Vaz Pérez A, *et al*, 2011). Regarding drug delivery technologies, technological developments for digoxin distribution are not well documented, although overall

breakthroughs in pharmaceutical delivery systems have the potential to improve the safety and effectiveness of drugs like digoxin. Active research areas that have the potential to transform medicine administration, enhance patient outcomes, and lessen adverse effects comprise controlled-release formulations, the field of nanotechnology, and tailored medication delivery methods (Ezike *et al*, 2023).

Prediction for Digoxin's Future Use in Clinical Practice: Digoxin's future place in clinical practice is still up in the air because of conflicting data about its safety and effectiveness. Despite being used historically to treat heart diseases, digoxin has mostly been replaced as the initial option by newer pharmaceuticals with superior security profiles. Due to studies like the DIG trial's inability to clearly show a reduction in overall mortality, its continuation is being closely scrutinized (Virgadamo *et al*, 2015).

Interactions with Drugs:

Digoxin is prone to a wide range of drug interactions; 426 medications have been shown to interact with it. Important interactions include drugs like dronedarone, propafenone, macrolide antibiotics (erythromycin, clarithromycin), azole antifungals (itraconazole), St. John's wort and a number of cardiac rhythms drugs. Digoxin also interacts with blood pressure drugs, antibiotics, and diuretics. Additional interactions include drugs such as Cytotoxic drugs, sucralfate, acarbose, and enzyme inducers can alter digoxin's absorption or excretion.

Acute myocardial infarctions, ventricular arrhythmias, bradyarrhythmia's, AV blocks, hypercalcemia, hypokalaemia, hypomagnesemia, preserved left ventricular ejection fraction, renal dysfunction, vasoconstriction, thiamine deficiency, hyperthyroidism, hypothyroidism, and specific drugs taken during pregnancy or lactation are among the disorders that interact with one another. Keeping medical professionals informed about all prescription and over-the-counter medications is crucial in reducing the risk of problems resulting from drug interactions.

Reports of digoxin toxicity have been attributed to the Observing drugs:

Amiodarone: Reduces the renal and nonrenal clearance of digoxin and may increase heart rate. A few isolated instances of digoxin poisoning have been connected to the benzodiazepine's diazepam and alprazolam. Digoxin blood levels may increase as a result of cardiogenol in addition to its heart rate-inducing effects. Beta-blockers like metoprolol and atenolol may have additive effects on heart rate.

Calcium channel blockers: Diltiazem and verapamil increase serum digoxin levels; however not all calcium channel inhibitors have the same impact. Digoxin levels may rise when using cyclosporine, most likely as a result of reduced renal excretion. Erythromycin, clarithromycin, and tetracyclines can all raise digoxin levels.

Conclusion

The use of herbal gel is becoming increasingly common. Digitalis is a very useful treatment for chronic valvular cardiomyopathy with failed or broken compensation. It must be taken cautiously, nevertheless, keeping in mind the need in situations of dropsy, insufficient urine, and a weak, fast, and irregular pulse. Heart glycosides are a broad category that is secondary compounds with a variety of applications that are created by various natural processes. Depending on arrangement of the unsaturated lactone ring in the aglycone, cardiac glycosides can contain either cardenolides or bufadienolides. In Africa, many therapeutic Herbs are utilized to address a variety of ailments. These plants have previously yielded some cardiac glycoside metabolites with promising medication characteristics, such as toxic to the brain, anti-inflammatory in nature enzyme-inhibitory, antimicrobial, cytotoxic, and markers against coronary heart diseases, which are classified as non-communicable diseases. It's important to remember that the most prevalent plant groups in cardiac glycosides are Apocynaceae and Asclepiadaceae. When arterial hyperemia is visible and cardiac hypertrophy exceeds dilatation, digitalis is likely to exacerbate the condition or result in further issues. Foxglove, is a significant therapeutic ingredient that is a member of the Scrophulariaceae family. It is indigenous to Europe and the northwest region of Africa (Morocco). Its leaves are used to cure ailments such as palpitations, ascites, infections, influenza, persistent pleurisy, menstrual bleeding, and seizures, burns, as well as left ventricular hypertrophy about the heart. They also have cardio-tonic, diuretic, sedative, hemostatic, and antipyretic qualities. In the absence of significant heart degeneration or pericardial adhesions that would restrict its effects, mitral insufficiency and regurgitation are undoubtedly the optimum conditions for digitalis therapy to function. The sodium/ potassium. But it appears that many flavonoids have despite the beneficial pharmacological effects of this class of secondary metabolites, some of these compounds have been demonstrated to be harmful. The potential of several of these compounds for use in medicine may be significantly limited by their detrimental side effects. It mostly increases the heart's contractility to achieve this goal. The World Health Organization (WHO) estimates that one billion people, or a percentage of the world's population, presently receive basic healthcare. Through herbal medicine. A significant part of the traditional medical practices of all indigenous peoples includes herbal medicine in addition to systems of Ayurveda, homeopathy, naturopathy, and traditional oriental medicine. Different chemicals are used in the various types of digitalis drugs compositions. Subsequent investigations regarding potential modifications regarding the chemical structures of these cardiac glycosides to reduce their toxicity and enhance their structural activity correlations may prove valuable. Digoxin's continued relevance and roots in technological advances serve as a painful reminder of the mutually beneficial among innovation and tradition in striving of the best possible outcomes for patients as we negotiate the complexity of cardiovascular treatment. It is assumed that the debate over digitalis and its use will become less heated when new medications are developed that highlight life expectancy as a major outcome, even in the absence of a definite assertion of victory from either side.

Reference

X.S. Li, M.J. Hu, J. Liu, Q. Liu, Z.X. Huang, S.L. Li, X.J. Hao, X.K. Zhang, X.S. Yao, J.S. Tang, (2014) Cardiac glycosides from the bark of antiaris toxicaria, Fitoterapia 97,71–77

R. Lutembacher, J. De Luna,(1947) , Bull. Med. 61,453–460.

R.C. Batterman, A.C. De Graff, (1947) Comparative study on the use of the purified digitalis glycosides, digoxin, digitoxin, and lanatoside c, for the management of ambulatory patients with congestive heart failure, Am. Heart J. 34,663–673.

A. Hollman, (1996) Drugs for atrial fibrillation. Digoxin comes from *Digitalis lanata*, BMJ 312 ,912.

K.L. Yeau, H. Whong, C.K. Wong, (1965) (The pharmacology of oleandrin compared with g-strophanthin, digoxin and digitoxin), Yao Xue Xue Bao 12 ,180–184.

L.M. Blum, F. Rieders, (1987) Oleandrin distribution in a fatality from rectal and oral nerium oleander extract administration, J. Anal. Toxicol. 11, 219–221.)

P.S. Steyn, F.R. van Heerden,(1998) Bufadienolides of plant and animal origin, Nat. Prod. Rep. 15,397–413.

T. Eisner, D.F. Wiemer, L.W. Haynes, J. Meinwald, Lucibufagins: (1978) Defensive steroids from the fireflies photinus ignitus and p. Marginellus (coleoptera: Lampyridae), Proc Natl Acad Sci U S A 75 ,905–908

D.A. Hutchinson, A.H. Savitzky, G.M. Burghardt, C. Nguyen, J. Meinwald, F.C. Schroeder, A. Mori, (1987) Chemical defense of an asian snake reflects local availability of toxic prey and hatchling diet, J. Zool. 2013 (289) 270–278.).

Bricknell C, (Ed.). 2003. The royal horticultural society A-Z encyclopaedia of garden plant. Dorling Kindersley, London, England.

Willis AJ, Memmott J, Forrester RI. (2000). Is there evidence for the post invasion evolution of increased size among invasive plant species? Ecology Letters 3, 275–283.

Webb CJ, Sykes WR, Garnock-Jones PJ (1988). Flora of New Zealand: Naturalised pteridophytes, gymnosperms, dicotyledons. Botany Division, D.S.I.R, Christchurch, N.Z

Cameron PJ, Hill RL, Bain J, Thomas WP, (1989). A review of biological control of invertebrate pests and weeds in New Zealand 1874 to 1987. CAB International Institute of Biological Control, Wallingford, England; DSIR Entomology Division, Auckland.).

Sonya G Gordon, Mark D Kittleson,(2008) in Small Animal Clinical Pharmacology (Second Edition)

M. Bartnik, P.C. Facey, (2017) in Pharmacognosy

Priyanka Dashrath Deshmane,(2022)Digitalis Review: A Complete Pharmacognostic & Pharmacological Overview, International Journal of Current Research Trends (IJCRT).

Currie GM, Wheat JM, Kiat H: (2011)Pharmacokinetic considerations for digoxin in older people . Open Cardiovasc Med J. , 5:130-5. 10.2174/1874192401105010130

David MN, Shetty M: (2024)Digoxin. StatPearls Publishing, Treasure Island, FL.

Hausner, H., Derving Karsbøl, J., Holst, A.G., Jacobsen, J.B., Wagner, F.D., Golor, G., Anderson, T.W., (2017). Effect of semaglutide on the pharmacokinetics of metformin, warfarin, atorvastatin, and digoxin in healthy subjects. Clin. Pharmacokinet. 56 (11), 1391–1401.

Saunders, N.R., Dziegielewska, K.M., Møllgård, K., Habgood, M.D., (2019). Recent developments in understanding barrier mechanisms in the developing brain: drugs and drug transporters in pregnancy, susceptibility or protection in the fetal brain? Annu. Rev. Pharmacol. 59, 487–505.).

Chen S, Li S: The Na+/Ca²+ exchanger in cardiac ischemia/reperfusion injury. Med Sci Monit. (2012), 18:RA161-5. 10.12659/msm.883533

Komatsu, T., Morita, M., Miyaji, F., Inomata, T., Ako, J., Atsuda, K., (2015). Population pharmacokinetics and optimization of the dosing regimen of digoxin in adult patients. J. Pharm. Health Care Sci. 1, 25.

Gheorghiade M, Adams KF Jr, Colucci WS: (2004) Digoxin in the management of cardiovascular disorders. Circulation.109:2959-64. 10.1161/01.CIR.0000132482.95686.87

Heidenreich PA, Bozkurt B, Aguilar D, *et al*.: (2022) AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation. 2022, 145: e895-e1032. 10.1161/CIR.0000000000001063.

Negi SJ, Bisht VK, Bhandari AK and Sundriyal RC (2012). Determination of mineral contents of *Digitalis purpurea* L. and *Digitalis lanata* Ehrh. Journal of Soil Science and Plant Nutrition; 12: 469. 26.

Whalen K, Finkel R and Panavelil TA (2015). Lippincott illustrated reviews: Pharmacology, Wolters Kluwer, Edition 6th, 263-265. 27**Smith TW 1989. The fundamental mechanism of inotropic action of Digitalis. Therapie; 44: 431-435. 28.

Jorgensen PL, Hakansson KO and Karlish SJ (2003). Structure and mechanism of Na, K-ATPase: functional sites and their interactions. Annu Rev Physiol; 65: 817-849.)

Lee JY, Woo E and Kang KW (2006). Screening of new chemopreventive compounds from *Digitalis purpurea*. Pharmazie; 61(4): 356-358.).

Guntert TW, Linde HHA: (1981) Chemistry and structure-activity relationships of cardioactive steroids, In Greeff K (ed) Handbook of Pharmacology, Vol 56. Part 1: Cardiac Glycosides. Berlin: Springer-Verlag, pp 13–24.

Jowett N. (2002). Foxglove poisoning. Hosp Med. 63(12):758-759.12512208,

Lacassie E, Marquet P, Martin-Dupont S, Gaulier JM, Lachâtre G. (2000). A non-fatal case of intoxication with foxglove, documented by means of liquid chromatography-electrospray-mass spectrometry. J Forensic Sci. 45(5):1154-1158.11005196.

Lin CC, Yang CC, Phua DH, Deng JF, Lu LH. (2010). An outbreak of foxglove leaf poisoning. J Chin Med Assoc. 73(2):97- 100.20171590

Dick M, Curwin J, Tepper D. (1991). Digitalis intoxication recognition and management. J Clin Pharmacol.31(5):444- 447.2050830

Hauptman PJ, Kelly RA. (1999). Digitalis. Circulation. 99(9):1265-1270.10069797

Morton JF. (1977). Major Medicinal Plants. Springfield, IL: Charles C. Thomas.)

Bricknell C, (Ed.). (2003). The royal horticultural society A-Z encyclopedia of garden plant. Dorling Kindersley, London, England.

Lyon, (2016) IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some Drugs and Herbal Products. France: International Agency for Research on Cancer; Exposure Data. (Google Scholar).

Navarro E, Alonso SJ, Trujillo J. (2000) Cardiovascular Activity of a Methanolic Extract of *Digitalis purpurea* spp. Journal of Ethnopharmacology.;71(3):437-442.)

Rabadia J., 2014, Hepatoprotective Activity of Aqueous Extract of *Digitalis purpurea* in Carbon Tetrachloride Induced Hepatotoxicity in Albino Rats. Asian Journal of Biomedical and Pharmaceutical Sciences; 4(34):64- 71.).

Pervaiz MH, Dickinson MG, Yamani M: (2006) Is digoxin a drug of the past? Cleve Clin J Med. , 73:829-32. 10.3949/ccjm.73.9.821

Virgadamo S, Charnigo R, Darrat Y, Morales G, Elayi CS: (2015) Digoxin: a systematic review in atrial fibrillation, congestive heart failure and post-myocardial infarction. World J Cardiol. , 7:808-16. 10.4330/wjc.v7.i11.808

David MN, Shetty M:(2024) Digoxin. StatPearls Publishing, Treasure Island, FL.

Petrovna PG, Andreevna KL, Borisovna PS. (2023) UDC 616.12-008.46- 085: 612.396 MODERN APPROACH TO THE TREATMENT OF GLYCOSIDE INTOXICATION. In The 8 th International Scientific and practical conference "Scientific Research in the modern world"(June 1-3, 2023) Perfect Publishing, Toronto, Canada. . 639 p. 2023 Jun 1 (p. 40).)

Ziff OJ, Kotecha D: (2016) Digoxin: the good and the bad . Trends Cardiovasc Med. , 26:585-95. 10.1016/j.tcm.2016.03.011).

Sapna F, Raveena F, Chandio M, *et al.*(2023) Advancements in heart failure management: a comprehensive narrative review of emerging therapies. Cureus. , 15:e46486. 10.7759/cureus.46486).

Chang KY, Giorgio K, Schmitz K, *et al.*(2023) Effect of chronic digoxin use on mortality and heart failure hospitalization in pulmonary arterial hypertension. J Am Heart Assoc.,12:e027559.10.1161/JAHA.122.027559).

Vaz Pérez A, Turan RG, Rauchhaus M, (2011) Digoxin in chronic heart failure: possibility of a second chance?, QJM. , 104:369-71. 10.1093/qjmed/hcq197.

Ezike TC, Okpala US, Onoja UL, *et al.*(2023) Advances in drug delivery systems, challenges and future directions . Heliyon. , 9:e17488. 10.1016/j.heliyon.2023.e17488.

Virgadamo S, Charnigo R, Darrat Y, Morales G, Elayi CS, (2015 Digoxin: a systematic review in atrial fibrillation, congestive heart failure and post-myocardial infarction. World J Cardiol. , 7:808-16. 10.4330/wjc.v7.i11.808).

Chang KY, Giorgio K, Schmitz K, *et al*. J Am Heart Assoc. (2023); Effect of chronic digoxin use on mortality and heart failure hospitalization in pulmonary arterial hypertension. 12:0. doi: 10.1161/JAHA.122.027559.

Currie GM, Wheat JM, Kiat H: (2011) Pharmacokinetic considerations for digoxin in older people. Open Cardiovasc Med J. , 5:130-5. 10.2174/1874192401105010130.

Gona SR, Rosenberg J, Fyffe-Freil RC, Kozakiewicz JM, Money ME: (2023) Review: failure of current digoxin monitoring for toxicity: new monitoring recommendations to maintain therapeutic levels for efficacy. Front Cardiovasc Med. , 10:1179892. 10.3389/fcvm.1179892.

Abdel Jalil MH, Abdullah N, Alsous MM, Saleh M, Abu-Hammour K, (2020) A systematic review of population pharmacokinetic analyses of digoxin in the paediatric population. Br J Clin Pharmacol. , 86:1267-80. 10.1111/bcp.14272.

Hirai T, Kasai H, Naganuma M, Hagiwara N, Shiga T: (2022) Population pharmacokinetic analysis and dosage recommendations for digoxin in Japanese patients with atrial fibrillation and heart failure using real-world data. BMC Pharmacol Toxicol. , 23:14.

Dasgupta A: (2016) Chapter 4 - monitoring free drug concentration: clinical usefulness and analytical challenges. Clinical Challenges in Therapeutic Drug Monitoring. Clarke W, Dasgupta A (ed): Elsevier, San Diego.

Pervaiz MH, Dickinson MG, Yamani M: (2006) Is digoxin a drug of the past? Cleve Clin J Med., 73:829-32. 10.3949/ccjm.73.9.821.