EVALUATION OF PHARMACOLOGICAL PROFILES OF CARDIAC GLYCOSIDE

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ABSTRACT

Cardiac Glycoside is a class of molecule with promising pharmacological activities across various therapeutic areas.This abstract provides a concise overview of cardiac glycoside, its pharmacological actions and recent advancements, and future prospects. The pharmacological evaluation of Cardiac Glycoside spans various therapeutic area including, cardiovascular activities like congestive heart failure, antiarrhythmic, atrial fibrillation and the recent advancement in cytotoxicity, antiproliferative, anticancer action. Further research is conducting regarding the antiviral and antitumour activity of cardiac Glycoside

KEYWORDS

Antiarrhythmic, Anticancer, Cardenolides, Cardiac Glycoside, Congestive heart failure, Digitalis, Digoxin

INTRODUCTION

Cardiac glycosides are naturally occurring bioactive compounds. They are derived from several plant species including the foxglove (*Digitalis purpurea*), yellow oleander (*Thevetin peruviana*), and climbing oleander (glycosides consist of two main components: aglycone and glycone. Aglycones are usually steroids, while glycone are sugars [2] Several cardiac glycosides are used in cardiology for the treatment of cardiac congestion and some types of cardiac arrhythmias. Over the years, several reports have suggested that cardiac glycosides may have an anticancer utilization [3]

CHEMISTRY OF CARDIAC GLYCOSIDE

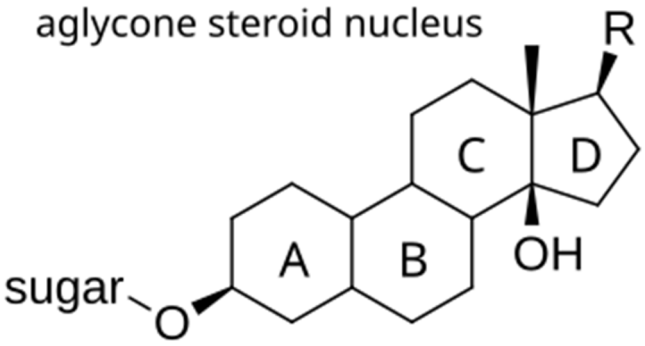


FIG.1 Chemistry of cardiac Glycoside

The chemical structure of cardiac glycosides consists of a sugar residue, an unsaturated lactone ring (5 atoms) and a steroidal residue (Fig. 1). The isoform devoid of a sugar moiety is called an aglycone. Depending on the number of atoms in the lactone ring, glycosides are divided into cardenolides (five-atom lactone) and bufadienolides (six-atom lactone) [4]The steroid group is common to all substances, consisting of 17 carbons distributed in four rings connected to a lactone ring and different sugar residues. The most frequently found sugars are glucose, galactose, mannose, rhamnose, and digitalize. CG activity is related to the lactone ring, while sugar residues are a determinant for the toxicokinetic and toxicodynamic of each substance [5]

CLASSIFICATION

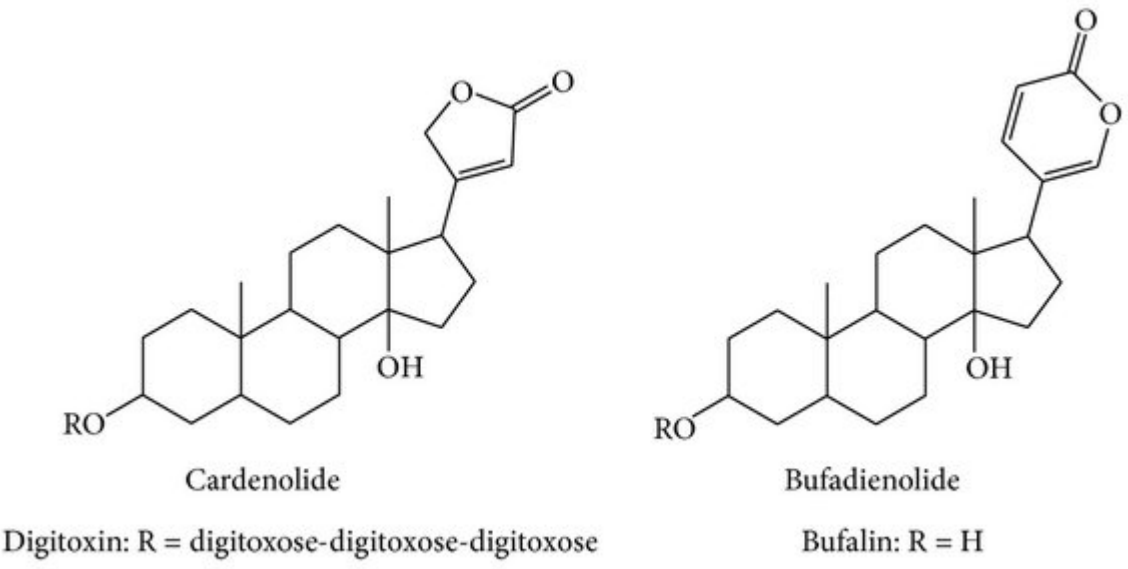


FIG.2. classification [6]

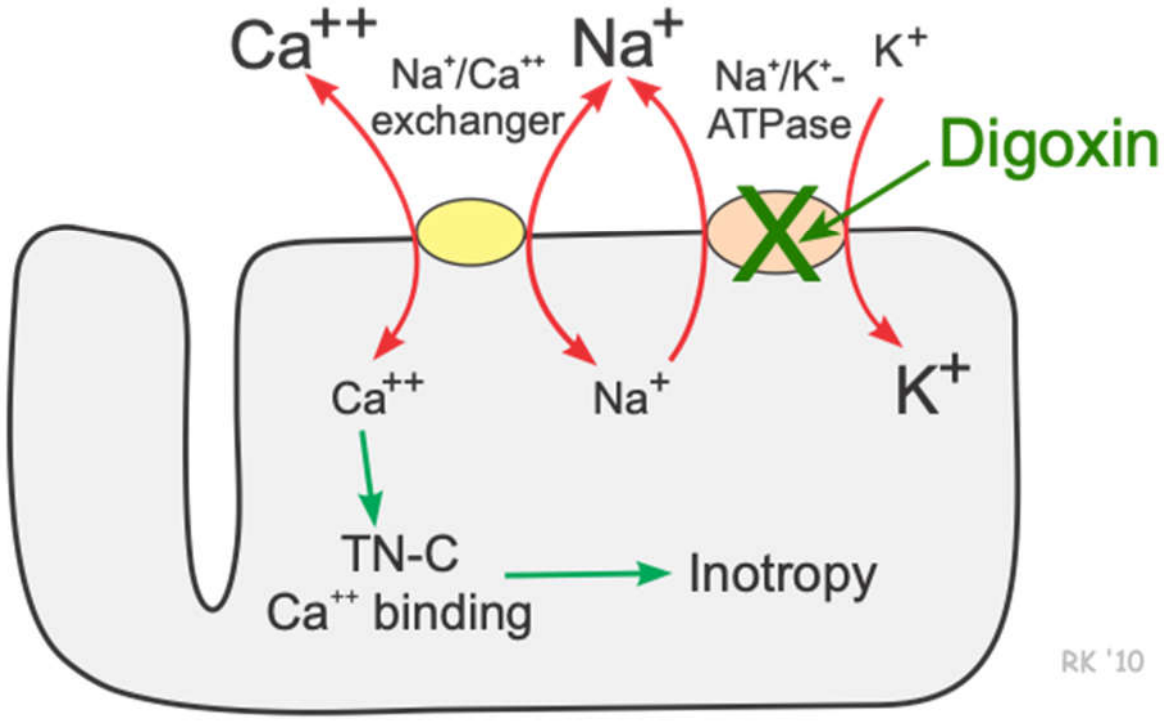
MECHANISM OF ACTION OF CARDENOLIDES

Digitalis compounds are potent inhibitors of cellular Na^+/K^+-ATPase. This ion transport system moves sodium ions out of the cell and brings potassium ions into the cell. The Na^+/K^+-

ATPase also plays an active role in membrane potential generation. it transports 3 sodium ions out of the cell for every two potassium ions that enter the cell.

cells, have a Na^{+}-Ca^{++} exchanger that is essential for maintaining sodium and calcium homeostasis. Furthermore, three sodium ions are exchanged for each calcium, therefore an electrogenic potential is generated by this exchanger. An increase in intracellular sodium concentration competes for calcium through this exchange mechanism, leading to an increase in intracellular calcium concentration. As intracellular sodium increases, the concentration gradient driving sodium into the cell across the exchanger is reduced, thereby reducing the activity of the exchanger, which decreases the movement of calcium out of the cell. Therefore, mechanisms that lead to an accumulation of intracellular sodium cause a subsequent accumulation of intracellular calcium because of decreased exchange pump activity.

By inhibiting the Na^{+}/K^{+}- ATPase, cardiac glycosides such as digoxin cause intracellular sodium concentration to increase. This leads to an accumulation of intracellular calcium via the Na^{+}- Ca^{++} exchanger. In the heart, increased intracellular calcium causes more calcium to be taken up and subsequently released by the sarcoplasmic reticulum, thereby making more calcium available to bind to troponin-C, which increases contractility (inotropy). Inhibition of the Na^{+}/K^{+}- ATPase in vascular smooth muscle causes depolarization, which causes smooth muscle contraction and vasoconstriction.[7]



Mechanism of action of cardenolides[FIG] 3

EXTRACTION OF CARDIAC GLYCOSIDE

Extraction of cardiac glycosides from natural materials, such as plant leaves or flowers, involves several major steps including material collection, sample preparation, extraction, and purification. Following are the details of these steps:

1. Collection of Plant Material plant Which containing cardiac glycosides, such as Digitalis purpurea or Nerium oleander leaves, should be collected at the right time, usually when the glycoside content reaches its peak.

2. Sample Preparation a. Drying Fresh plant material is dried in a shady, well-ventilated area to prevent degradation of the active compounds. This drying can be done naturally or by using an oven at a low temperature (40-50°C).

b. Milling Once dry, the plant material is ground into a fine powder to increase surface area and extraction efficiency.

3. Extraction

a. Extraction Solvent Organic solvents such as ethanol, methanol, or a mixture of water and ethanol are used to extract cardiac glycosides from plant powders. The choice of solvent depends on the solubility of the cardiac glycoside in the solvent.

b. Extraction Process Extraction can be done by several methods: Maceration The plant powder is soaked in the solvent at room temperature for several days with periodic stirring. Soxhlation The plant powder is extracted continuously with a hot solvent using a Soxhlet device for several hours.

Ultrasonication Use ultrasonic waves to speed up the extraction process by breaking down plant cells and releasing cardiac glycosides into the solvent.

Filtration Once the extraction process is complete, the mixture is filtered to separate the liquid extract from the plant dregs

. 4. Purification a. Solvent Evaporation Liquid extract obtained from filtration Then evaporated using a rotary evaporator to remove the solvent and obtain a concentrated extract.

b. Fractionation The concentrated extract is then further separated using chromatography techniques, such as: Column Chromatography The extract is flowed through a column containing a stationary phase (silica gel or resin) and separated based on differences in polarity.

High Performance Liquid Chromatography (HPLC) Uses high pressure to separate extract components with high resolution and faster speed.

5. Identification and Characterization The cardiac glycoside components in the purified extract were identified using spectroscopic techniques such as UV-Vis, IR, NMR, and MS to determine the structure and purity of the compound

. 6. Biological Activity Test Biochemical Test The biological activity of extracts containing cardiac glycosides was tested to ensure effectiveness and safety. This test can include testing the activity of the Na+/K+-ATPase enzyme or in vitro and in vivo animal studies [8]

DETERMINATION OF CARDIAC GLYICOSIDE

Digoxin is most frequently determined with the use of radioimmunological and immunoenzymatically methods. Reagents required for these methods are available on the market. The concentrations of digoxin presented in the literature, determined in autopsy blood taken from persons who were treated with this compound, are very varied. Values of these concentrations depend on the analytical methods used for their determination and the place from which blood was taken for analysis. In serum of blood taken from the right heart ventricle, the concentrations of digoxin were in the range of 0.5–2.1 g/l; the mean value being 1.3 g/l in 18 cases. At the same time a significant decrease of the concentration of digoxin was observed in this material, caused by haemolysis of blood during determination of this compound by the radioimmunological method. In spite of the high specificity of immunoenzymatically techniques – thanks to the antibodies used – there are numerous known cases of false positive results. One of the causes of this is formation of endogenic substances in an organism in vivo and post-mortem, immunoreacting with the antibodies present in the applied test. Other techniques such as thin layer chromatography (TLC), high pressure liquid chromatography with spectrophotometric detection (HPLC-UVD) and high-pressure liquid chromatography with fluorescence detection [9]

IDENTIFICATION TEST

The following are the identification tests for Cardiac Glycosides [10]

1.Xanthydrol test The crude is heated with 0.1-5% of xanthydrol in glacial acetic acid containing 1% hydrochloric acid	A red colour is produced	Presence of deoxy sugar
2..Baljet test Take piece of lamina or thick section of leaf. Add sodium picrate reagent	Yellow to orange colour	Presence of glycoside
3.kedde test A solution of glycoside is treated with kedde's reagent (mix equal volume of 2%	Development of blue or violet colour that faded away in 1 to 2 hr	Presence of cazdenolide

solution of 3,5 dinitro benzoic acid in methanol and 7.5% aqueous solution of KOH)		
4.Antimony trichloride test To a solution of glycoside add a solution of Antimony trichloride and trichloro acetic acid and then heat the mixture	Appearance of blue or violet colour	Presence of cardenolides and bufadienolides
5.Keller killiani test Glycoside is dissolved in a mixture of 1% ferric sulphate in 5% glacial acetic acid. Add one to two drops of concentrated sulphuric acid.	A blue colour develops	Presence of deoxy sugar

BIOACTIVITY

1. Cardiotonic property
a. Arrythmia and Congestive heart failure

Cardiac glycosides have long served as the main medical treatment to cardiac failure and cardiac arrythmia, due to their effects of increasing the force of muscle contraction while reducing heart rate. Heart failure is characterized by an inability to pump enough blood to support the body, possibly due to a decrease in the volume of the blood or its contractile force [10]Cardiac glycosides inhibit the sodium-potassium adenosine triphosphatase (Na^+/K^+ ATPase) exchanger in cardiomyocytes – which leads to a decreased heart rate and increased cardiac contractility.[11] Cardiac glycosides, such as the commonly used digoxin and digitoxin, deal with the latter, due to their positive ionotropic activity. A medicine with a

similar action to digoxin is its structural analogue – methyldigoxin, a cordial glucoside obtained semi synthetically. In comparison to digoxin, methyldigoxin acts much faster:[9] On the other hand, cardiac arrhythmia are changes in heart rate, whether faster (tachycardia) or slower (bradycardia). Medicinal treatments for this condition work primarily to counteract tachycardia by slowing down heart rate, as done by cardiac glycosides [12]

B. Atrial fibrillation and flutter

Atrial fibrillation and flutter lead to a rapid ventricular rate that can impair ventricular filling (due to decreased filling time) and reduce cardiac output. Furthermore, chronic ventricular tachycardia can lead to heart failure. Digoxin, although not a first-line drug for rate control, can be used to reduce ventricular rate when a high atrial rate or atrial fibrillation is driving it. The mechanism of this beneficial effect of digoxin is its ability to activate vagal efferent nerves to the heart (parasympathomimetic effect). Vagal activation can reduce the conduction of electrical impulses within the atrioventricular node to the point where some impulses will be blocked. When this occurs, fewer impulses reach the ventricles and the ventricular rate falls. Digoxin also increases the effective refractory period within the atrioventricular node.[13]

2. Anti-Proliferative and Cytotoxic Effects of Cardiac Glycosides

- Uncontrolled cell proliferation is considered as a significant hallmark of cancer cells. Cancer progression is characterized by continuing cell proliferation leading to tumour development and rapid expansion. The cancer cells can also evade the growth suppressors and antiproliferative signals, which drive inadequate cell division and dysregulate tissue homeostasis. Several studies have highlighted the antiproliferative activity of Cardiac glycoside drugs on different cancer cells. Bufalin showed antiproliferation against human melanoma BRO cells by arresting them. Recently Silva et demonstrated that Amantdig, a semisynthetic cardenolide derivative of digitoxigenin, in combination with docetaxel exhibited a synergistic anti-proliferative effect on human androgen-insensitive prostate cancer cells. The antiproliferative effect of ouabain in human breast (BT20) and prostate (DU145) cancer cell lines. The inhibitory effect of digitoxin, digoxin, and ouabain was reported on the androgen-dependent LNCaP, androgen-independent DU145, and PC3 cells in a dose and time-dependent manner. Of these three Cardiac Glycoside, ouabain more effectively exerted its antiproliferative effect on prostate cancer cells than digoxin and digitoxin. Proscillaridin is the most potent and cytotoxic compound, followed by digitoxin, ouabain, digoxin, and lanatoside C. Both digitoxin and digoxin exhibited selective cytotoxicity against the solid tumour cells. In contrast, proscillaridin . A lacked selective cytotoxicity towards solid and haematological tumour cells. [13]

2.cardiac Glycoside as cancer Therapeutics

Over the years, several reports have documented the cancer therapeutic potential of Cardiac Glycosides. The first epidemiological evidence regarding the anticancer effect of Cardiac Glycosides was provided by Stenkvistetal. A series of studies confirmed that the breast cancer tissue samples obtained from the patients treated with digitalis Cardiac Glycoside therapy exhibited more delicate features than the cancer samples from control patients

without digitalis therapy. The risk of cancer recurrence post five years of mastectomy was 9.5times higher in the control patients without digitalis therapy than the patients treated with digitalis. The study indicated the significant impact of Cardiac Glycosides on the biological aggressiveness of breast cancer. Subsequently, Goldin and Safa, in1984, screened the effect of digitalis on the mortality rate of 127breast cancer patients. The study documented the death of 21 patients due to cancer, and among them, only one patient was previously treated with digitalis. The report confirmed the potential rate of digitalis in protecting against cancer.[13]

Cancer type	Cardiac glycoside used	Cell lines
Breast	Digoxin, digitoxin, oleandrin, lanatoside	MCF-7, MDA-MB-231, MDA-MB-435
Cervical	Digoxin, oleandrin, convallotoxin	HeLa
Colon	Digoxin, oleandrin, lanatoside C	SW480, HCT116, RKO, HT-29
Leukaemia	Digitoxin, UNBS1450	K56, U937
Prostate	Digitoxin, digoxin, ouabain, oleandrin	PC3, C4-2, DU-145, LNaP

Future prospects

1.Single-cell transcriptomic and proteomic data sets with high resolution may aid in generating reliable information on the effect of Cardiac Glycoside on cancer versus normal cells in various tumours. Furthermore, high throughput screening of Cardiac Glycoside using tumoroids and organoids may supplement preclinical Biomolecules 2021, 11, 1275 23 of 30 effectiveness and safety research. These technologies are expected to unravel the regular tory mechanisms that orchestrate the transcriptional processes regulating tumorigenesis. Among the large number of dysregulated oncogenic TFs, only a few have been successfully identified and targeted. These findings in coordination with gene-specific therapy could be the new paradigm for targeted cancer therapeutics. Thus, a comprehensive understanding of the transcriptional network proteins could potentially decipher the TFs mis regulation in cancer. Recent improvements in cryo-electron microscopy (cryoEM) have also opened up new avenues for understanding the structures of Cardiac Glycoside-protein interaction dynamics, which was difficult to dissect using traditional structural biology techniques. Future studies could focus on discovering novel TFs and pathways involved in the complex transcriptional network regulating tumorigenesis. Besides, improved algorithms and models for network analysis would substantially increase the probability of finding druggable TF targets. Bioprospecting of novel Cardia Glycoside and extensive studies may also uncover novel pathways to inhibit dysregulated TFs. [13]

2.growing number of recent efforts were focused on exploring the antitumor and antiviral potential of these compounds. Several reports suggest their antitumor properties and hence, today cardiac glycosides (CG) represent the most diversified naturally derived compounds strongly recommended for the treatment of various cancers. Mutated or dysregulated

transcription factors have also gained prominence as potential therapeutic targets that can be selectively targeted. Thus, we have explored the recent advances in Cardiac Glycosides mediated cancer scope and have considered various signalling pathways, molecular aberration, transcription factors (TFs), and oncogenic genes to highlight potential therapeutic targets in cancer management.[13]

CONCLUSION

Cardiac Glycoside has proven to highly effective and potent in a range of pharmacological application such as cardiotonic, anticancer, antiproliferative, cancer activities Cardia Glycoside is highly promising in pharmacological field because of their wide range of biological activity and possible therapeutic outcome. More research and development should be conducted in anticancer property and

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