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Plant-derived cardiac glycosides: Role in heart ailments and cancer management

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ABSTRACT

Cardiac glycosides, the cardiotonic steroids such as digitalis have been in use as heart ailment remedy since ages. They manipulate the renin-angiotensin axis to improve cardiac output. However; their safety and efficacy have come under scrutiny in recent times, as poisoning and accidental mortalities have been observed. In order to better understand and exploit them as cardiac ionotropes, studies are being pursued using different cardiac glycosides such as digitoxin, digoxin, ouabain, oleandrin etc. Several cardiac glycosides as peruvoside have shown promise in cancer control, especially ovary cancer and leukemia. Functional variability of these glycosides has revealed that not all cardiac glycosides are alike. Apart from their specific affinity to sodium-potassium ATPase, their therapeutic dosage and behavior in poly-morbidity conditions needs to be considered. This review presents a concise account of the key findings in recent years with adequate elaboration of the mechanisms. This compilation is expected to contribute towards management of cardiac, cancer, even viral ailments.

Contents

1. Introduction

Heart disease has become very common cause of morbidity and mortality in today's time [4,61]. High heart morbidities are arising due to sedentary and unhealthy lifestyles. These ailments manifest in myriad forms such as cardiac arrhythmia, congestive heart failure, atrial fibrillation etc. [70,58]. Heart failure is common in infectious diseases such as HIV, the causes being viral replication, mitochondrial dysfunction, cardiac autoimmunity etc. [25]. Other cardiac pathologies occur due to drugs, alcohol abuse, micronutrient deficiency, tobacco use, to name a few. Conventional therapy includes angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers [6], β-blockers [43], phosphodiesterase inhibitors, calcium sensitizers and mineralocorticoid receptor antagonists [78], in addition to device therapy (pacemakers, implantable cardioverter defibrillators (ICD), systems for cardiac resynchronization therapy (CRT)) [35].

A common therapy for heart ailments is cardiac glycosides [38]. Cardiac glycosides have been part of folk medicines since ages, as heart tonics, diuretics and emetics [38]. In various pharmacopoeia (Danish, German, Indian, Chinese (TCM) etc.), they are mentioned as tinctures, infusions, and tablets [8]. Also, they have been used as arrow smear [75], rodent poisons and for suicidal purposes [41].

Compared to cardiac roles, efficacy of cardiac glycosides against cancer is rather new. Anticancer scopes of these glycosides have

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been evaluated in recent times, that has generated promising data. Some cardiac glycosides such as digitoxin, digoxin, bufalin, and ouabain inhibit cancer cell proliferation and block tumor growth, by inducing immunogenic cell death [39]. Selective of them (such as digoxin) are undergoing clinical trials [13,63,66].

These plant secondary metabolites are glycosides (sugars) which manipulate the contractile force of cardiac muscles, contributing to their inotropic (ability to change heart contraction) functions [71]. Though they can heal heart pathologies, they can aggravate it to, leading to fatalities [71]. A number of plants possess cardiac glycosides such as *Antiaris toxicaria* (a Moraceae family plant) [56], *Asclepias* sp. [2], *Bowiea volubilis* (bowiea) [3], *Calotropis procera* [34], *Calotropis gigantea* (crown flower), *Convallaria majalis* (lily of the Valley) [86], *Digitalis purpurea* (foxglove) [49], *Drimia maritima* (sea onion) [45], *Kalanchoe daigremontiana* (devil's backbone) [10], *Nerium oleander* (oleander) [47], *Thevetia peruviana* (yellow oleander) [80], *Strophanthus* [44] etc. Most of them belong to Plantaginaceae, Apocyanaceae, Asparagaceae, and Moraceae family [11]. Apart from plants, insects like milkweed butterflies (*Danaus gilippus* and *Syntomeida epilais*) have these glycosides in their tissues [29]. Several cardiac glycosides have been isolated from amphibians as toads (*Bufo rubescens*, *Bufo marinus*) [77] and mammals (including human), such as digoxin, ouabain, bufalin, and telecinobufagin. The cardiac glycoside sources have been listed in Table 1. Well −characterized cardiac glycosides include digoxin, bufalin, ouabain, oleandrin, thevetin, convallatoxin, peruvoside, proceraside, antiaroside, antiaritoxiosides, strophanthidin, and antiarigenin etc. [47,66,74,56,19,20].

Cardiac glycosides are conjugates of a glycone and an aglycone part. Glycone moiety can be glucose, fructose, glucuronide, rutinose, rhamnose [54]. The aglycone part of cardiac glycoside is a steroidal nucleus [28]. Depending on the aglycone moiety, the glycosides can be of many types such as alcoholic (salicin); anthraquinone (antron and anthranol); coumarin; chromone; cyanogenic (amygdalin, linamarin, lotaustralin, dhurrin, prunasin); flavonoid (hesperidin, rutin, naringin); phenolic (e.g. arbutin); saponins (e.g. diosgenin, ginsenosides); cardiac; steviol (e.g. stevioside and rebaudioside A); iridoid (e.g. aucubin, geniposidic acid, theviridoside, loganin, catalpol); thio (e.g. sinigrin, sinalbin) etc. [17]. Glycoside hydrolases cleave the glycosidic bonds between the two moieties, where the bond can be of C-linkage, O-linkage, N-linkage or S-linkage type [7]. Based on the R group at the 17-position, cardiac glycosides can be classified into two types such as cardenolide with lactone 2-furanone (kalantubolide A, kalantubolide B) and bufadienolide type with lactone 2-pyrone (kalantuboside A, kalantuboside B) [55,48,32].

Plants use their glycosides (such as cyanopropenyl glycoside) as pesticides [40]. Cyanogenic glycosides from cassava roots, yams, maize, sorghum, almond, apricot, cherries etc. liberate cyanide, which blocks cytochrome C oxidase, leading to their increased release into the cytosol, a response against herbivory [24,68].

2. Mechanisms

Heart health is vital for survival, which undergoes the assault of renin-angiotensin-aldosterone system. Imbalance of electrolytes (hyponatremia, hypokalemia) and pH, results in heart abnormalities as cardiac arrhythmias. Therapeutics like diuretics, cardiac glycosides and ACE inhibitors has variable effects on heart muscles.

Na-K-ATPase (sodium-potassium) is an electrogenic pump located in the cell membrane that transports potassium ions in and sodium ions out [76]. This pump maintains ion gradients between cytoplasm and the extracellular fluid (ECF) by spending one ATP in exchange of three intracellular Na^+ ions and two extracellular K^+ ions [76,22]. This pump made of alpha ($\alpha1$–$\alpha4$) and beta ($\beta1$–$\beta3$) subunits occur is multiple isoforms [81]. The isozymes of the pump behave differently with variable physiologic conditions [76]. The cardiac glycosides inhibit these pumps on cardiac myocytes, preventing sodium exit from cell. Intracellular pooling of sodium ion prevents calcium exit as well. Higher concentration of cytoplasmic calcium enhances calcium uptake into the sarcoplasmic reticulum (SR) by the SERCA2 transporter [12]. On stimulation, sarcoplasmic reticulum releases high amount of calcium. It improves contractility of myocytes. Together, the ion buildup inside the cell increases cardiac output by increasing the force of contraction. The contractile acceleration is mediated by cross-bridge cycling [64]. The refractory period (time taken to recover from excitation) of the atrioventricular (AV) node is increased, thus regulating heart beat cycle [60]. Cardiac glycosides can increase heart output, but its intensity is unpredictable. Involved risk includes too high calcium level inside the cell due to high dosage of cardiac glycosides. It can lead to electrical instability, causing consequent ventricular tachycardia and fibrillation [53]. Ouabain, the cardiac glycoside made of rhamnose and ouabagenin activates Na-K-ATPase, triggering the release of intracellular calcium. It activates myocardial metabolism [23]. Ouabain stimulates cyclooxygenase −2 (COX-2) expression and a sustained protein kinase A (PKA) activation [50].

Though rather novel, an impressive body of the antineoplastic role of cardiac glycosides has been accumulated in recent times, some of which have been discussed here. Bufalin acts as a small-molecule inhibitor for steroid receptor coactivator (SRC-3 and SRC-1), and thus block cancer cell growth. The anticancer ability is traced to the Na-K-ATPase manipulation ability, as this pump has been the target of chemotherapy as well. This pump has been linked to cancer onset, proliferation and metastasis [31]. A study found that anticancer property of cardiac glycosides depend on the selectivity towards alpha subunits of the Na-K-ATPases on the plasma membrane [15]. Both ouabain and digitoxin inhibited migration ability of MDA-MB-231 breast cancer cells by manipulating the Na-K-ATPase antiport function [59]. A study on the effect of cardiac glycosides on human non-small cell lung cancer (NSCLC) cells revealed that the anticancer mechanism is by autophagy

Table 1
Botanical names of the cardiac glycoside-producing plant species, their common names, and families.

Species	Common name	Family/Class	Cardiac glycoside	References
Antiaris toxicaria	–	Moraceae	Antiaritoxioside	[56]
Asclepias sp.	Butterfly milkweed	Asclepiadaceae	–	[2]
Bowiea volubilis	Bowiea	Asparagaceae		[3]
Calotropis sp.	Crown flower	Apocynaceae	–	[34]
Convallaria majalis	Lily of the Valley	Asparagaceae	Convallatoxin	[86]
Digitalis purpurea	Foxglove	Plantaginaceae	Digoxin, gitoxin, digitonin,	[49]
Drimia maritima	Sea onion	Asparagaceae	–	[45]
Kalanchoe daigremontiana	Devil's backbone	Crassulaceae	Lanceotoxins	[10]
Nerium oleander	Oleander	Apocynaceae	Oleandrin, oleandroside, nerioside	[47]
Thevetia peruviana	Yellow oleander	Apocynaceae	Oleandrin	[80]
Strophanthus	–	Apocynaceae	Strophanthidin, periplogenin	[44]