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Review Article

Cardiac Glycosides from African Medicinal Plants as Promising Therapeutics

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ABSRTACT

Cardiac glycosides are a vast class of secondary chemicals found in nature from several sources and have a variety of applications. They also have a similar chemical structure. The present review aims to provide an updated review of cardiac glycosides isolated from African medicinal plants as promising therapeutics. The literature review used several internet resources, including Google, Google Scholar, PubMed, Medline, Research Gate, Web of Sciences, ScienceDirect, and SciFinder using the search terms "cardiac glycosides," "African medicinal plants," "natural products," "pharmacology," "isolated compounds," and "bioactivity". Cardiac glycosides are particularly prevalent in the families *Apocynaceae* and *Asclepiadaceae*. Several cardiac glycosides with known pharmacological properties, including cytotoxicity, antiviral, enzyme-inhibitory, anti-inflammatory, and neurotoxic properties, have been identified from African medicinal plants. Despite the numerous pharmacological activities of cardiac glycosides, the toxic side effects of several of these drugs may severely limit their therapeutic usage in humans. It was discovered that there was limited information on the isolation and characterisation of cardiac glycosides from plants in West Africa and the rest of the world while evaluating the literature on the pharmacological actions of cardiac glycosides. The lack of data on this molecule might result in knowledge extinction and prevent biological experiments on the secondary metabolite. Future studies should concentrate on the plants that have not yet been investigated to possibly isolate new cardiac glycosides and other kinds of chemicals. So, numerous biological functions may be tested on isolated molecules.

Keywords: Bioactive compounds, Cardiac glycosides, Medicinal plants, Pharmacology, Therapeutics

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Introduction

Secondary metabolites from plants are extremely useful in terms of the economy. These valuable chemicals are used in flavors, fragrances, medications, dyes, insecticides etc. Several secondary metabolites present in plants, including flavonoids, alkaloids, cardiac glycosides, terpenoids, and tannins, have been reported to have numerous pharmacological effects.[1,2] Plants have virtually limitless capacity to create aromatic chemicals, the bulk of which are phenols or their oxygen-substituted derivatives. Terpenoids are classified as secondary chemicals and are produced from the isopentenyl diphosphate (IPP), a molecule with five carbons.[3] There are around 12,000 recognized alkaloids in total, and all of them include a nitrogen atom or several that are produced by biosynthesis from amino acids.[4] A vast class of molecules found throughout nature, cardiac glycosides (CGs) are produced by 37 different plant and amphibian species.[5] Cardiac glycosides are made up of a sugar moiety, a lactone ring containing five or six carbons, and a steroid 40 ring, which is extremely similar.[6]

This review was aimed at providing detailed information about cardiac glycosides isolated from African medicinal plants and their various pharmacological activities. These plants could be further explored for drug discovery from natural sources.

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This group of compounds are natural steroids which are mainly found in plants such as foxgloves (*Digitalis sp.*) [7-8] or oleanders (*Nerium sp.*).[9] They are also found in animals, e.g., in the skin of toads.[10,11]

Cardiac glycosides (CGs) are naturally occurring compounds that have historically been used to treat heart conditions.[12,13] More recently, novel therapeutic applications have been suggested.[14] Cardiac glycosides are a large category of secondary compounds with a wide range of uses and a similar chemical structure found in nature from more than different sources. All cardiac glycosides contain a steroid ring connected to an unsaturated lactone ring in position 17, and many of them are related to a sugar moiety in position 3 as well.[15,16] This review on cardiac glycosides isolated from the African region will help broaden the scope of the importance of this secondary metabolite. It will also encourage further research into their isolation with great pharmacological activities, leading to drug discovery and development in Africa.

Methodology

Article search and selection

The search terms "cardiac glycosides," "African medicinal plants," "natural products," "pharmacology," "isolated compounds," and "bioactivity" were used to search for the literature for this review paper in several electronic sources, including PubMed, Google, Google Scholar, Medline, Research Gate, Web of Sciences, ScienceDirect, and SciFinder. The publications obtained were between 1965-2024. On April 4, 2024, these sources were last accessed. The search terms were used singly or in various combinations to obtain the most material feasible. The outcomes were carefully evaluated to make sure they met the criteria for inclusion. The publications, for example, must be written in English and focus on topics like the nomenclature and classification of cardiac glycosides, the distribution of cardiac glycosides in the plant kingdom, medicinal plants in Africa, and pharmacological activities of cardiac glycosides from African medicinal plants. Articles not provided in English are restricted from inclusion. The references to the papers

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were also looked at to uncover any prospective new research that was done correctly.

Results and Discussion

Classification and nomenclature of Cardiac Glycosides

Cardiac glycosides are glycosides of triterpene compounds, whose aglycones are derived from cyclopentanoperhydrophenanthrene and which have a particular impact on the heart muscle due to their unsaturated lactone ring at the C-17 position.[17] There are two forms of molecules in this category, depending on the structure of the unsaturated lactone ring of the aglycone (Figure 1). Cardenolides have a lactone ring with five members, while bufadienolides have a ring with six members.[18]

All cardiac glycosides have an unsaturated lactone ring bonded to a steroid ring in position 17, and many of them also have a sugar moiety attached to them in position 3 in addition to the common sugars (glucose, rhamnose)[19,20] (Figure 2).

Cardenolides and bufadienolides have the same solubility and foaming properties as steroid saponins and share a similar structural similarity.[21] Their skeleton has some peculiar sugar and a 14-hydroxy group, which set them apart from other steroid glycosides.

Digoxin, ouabain, oleandrin, and bufalin are the primary cardiac glycosides.[22] Table 1 displays the chemical formula, molecular weights, and sugar residues.

Distribution of Cardiac Glycosides in the Plant Kingdom

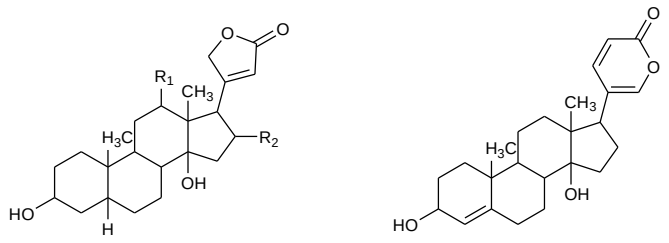
Small amounts of cardiac glycosides can be found in the bark, leaves, seeds, roots, and stems of many plants.[23] In the past, people from South America, Asia, and Africa used a variety of plants that grow in tropical areas to make arrow poisons.[24] The Cardenolides seem to be exclusive to angiosperms in plants. There are more of them in the *Apocynaceae* and *Asclepiadaceae* families (which are now included in the *Apocynaceae*).[25] Plant families *Apocynaceae* and *Asclepiadaceae* which are unique for Cardiac glycosides synthesis are the most prevalent Cardiac glycoside from African Medicinal Plants.

It may also be found in the plant families *Euphorbiaceae*, *Tiliaceae*, *Ranunculaceae*, *Moraceae*, *Leguminosae*, *Scrophulariaceae*, *Cruciferae*, *Sterculiaceae*, and *Liliaceae*. The medicinal plants and plant families that produce Cardenolides are shown in Table 2.

Bufadienolides are compounds found in plants from the *Crassulaceae*, *Iridaceae*, *Hyacinthaceae (Syn. Liliaceae)*, *Santalaceae*, *Melianthaceae*, and *Ranunculaceae* families.[26] They are known to be produced by the *Hyacinthaceae* genera *Urginea* and *Bowiea*. *Urginea maritima* (L.) Baker (*Hyacinthaceae*), often known as the squill, has produced several bufadienolide chemicals.[27] It is significant to note that the powerful digitalis-like effects of the six species that make up the genus *Urginea* have been used in medicine for a long time. Bufadienolides come from a variety of animal sources, including Buffo (toads), Rhabdophis (snakes), and Photinus (fireflies).[28] The chemical structures of isolated cardiac glycosides from African medicinal plants are shown in Figure 3.

Chemical test for Cardiac Glycosides

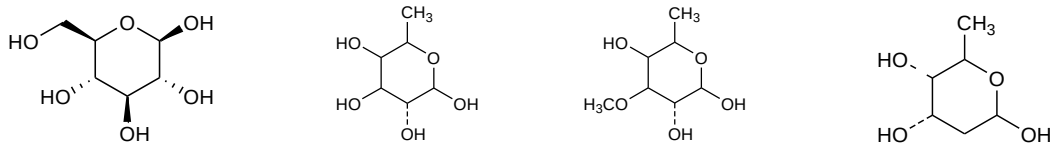
Cardiac glycosides exhibit color changes when combined with certain chemicals. Spray reagents can be applied on TLC which can be for both qualitative and quantitative applications. Antimony trichloride is used to test for both the cardenolides and the bufadienolides. When heated with antimony trichloride and trichloracetic acid, many of these glycosides change color to blue or violet. Legal test, Raymond test, kedde reagent, and Tollens test are used to test for the aglycone moiety while keller-kiliani test and xanthydrol test are used to test for sugars.[29]



Cardenolide Bufadienolide

Where R = a sugar residue

Figure 1: Structures of Aglycone Cardenolides and Bufadienolides of Cardiac glycosides



1. D-glucose 2. D-fucose 3. D-digitalose 4. D-digitoxose

Figure 2 Structures of some of the sugars present in cardiac glycoside compounds

Table 1: Main cardiac glycosides with their chemical formula, molecular weights, and sugar residues

S/N	Cardiac glycosides	Chemical formula	Molecular weight (g/mol)	Sugar moiety
1	Digoxin	$C_{41}H_{64}O_{14}$	780.949	Hexopyranosyl polysaccharides
2	Ouabain	$C_{29}H_{44}O_{12}$	584.659	Mannopyranosyl monosaccharide
3	Oleandrin	$C_{32}H_{48}O_9$	576.727	Hexopyranosyl monosaccharide and acetoxyl
4	Bufalin	$C_{24}H_{34}O_4$	386.532	Absent

The quantitative methods for cardiac glycosides comprise: Gravimetric, Colorimetric, Fluorimetric, RP-HPLC with UV or fluorometric detector, biological methods by determining the LD_{50}, and Immunoassay.

Medicinal plants in Africa

From the food business to the fragrance and cosmetics sector to different medical and pharmaceutical procedures, medicinal plants play an admirable and essential function in a range of scientific areas.[30] Medicinal plants play a significant role in many scientific domains and are crucial to human survival.[31,32] Previous research has indicated that plant materials include several useful natural chemicals, including alkaloids, flavonoids, coumarins, and iridoids.[33,34]

The ancient practice of using medicinal herbs, often known as traditional medicine (TM), is one of the most significant components of African culture. One of the oldest and most distinctive systems in the world is African TM.[35,36] Africa is endowed with an abundance of plant resources, with an estimated 40–45,000 species, 5,000 of which are utilized medicinally.[19] Due to the existing climatic circumstances, the African continent is marvelously endowed with a wide variety of plants.[37,38] This benefit has encouraged the abundance of secondary metabolites in the plants, which have helped them survive in hard environments.[39,40] African medicinal plants have given rise to several patents, and formulations (tinctures, teas, and infusions) made from them are used in rich and developing countries alike.[41] To expand the range of pharmacological products available for human use, it is imperative to search for novel pharmaceuticals derived from natural sources.[42]

Pharmacological activities of cardiac glycosides from African medicinal plants

The pharmacological activities of cardiac glycoside from African medicinal plants are summarized in Table 3. These include cytotoxicity, anti-viral, enzyme-inhibitory activity, anti-inflammatory, and neurotoxic activities.

Cytotoxic Activity of cardiac glycosides Identified in African Medicinal Plants

Continuous cell proliferation that results in tumor formation and fast growth are characteristics of cancer progression.[43] Cancer cells do not require external stimulators such as growth factors for their growth and division, in contrast to normal cells.[43] Cardiac glycosides (CG) are now the most varied naturally occurring substances that are highly recommended for the treatment of several cancers.[43] The proliferation of several types of cancer cells has been repeatedly shown to be inhibited by cardiac glycosides in recent years. Even clinical trials for the treatment of cancer have begun using some cardiac glycosides or their derivatives.[15,44] Anvirzel, a water extract from oleander, was the first cardiac glycoside examined in an anticancer clinical study and showed substantial anticancer action against a variety of malignancies with few side effects.[45-47] Cardiac glycosides isolated from *Thevetia peruviana* (Pers.) K. Schum. (Family *Apocynaceae*) were assayed for their cytotoxic potentials employing three distinct cancer cell lines namely human gastric (MGC-803), pancreatic (SW1990), and lung (P15) cancer and normal hepatocyte (LO2) cell lines. The compounds showed inhibition with IC_{50} values ranging from 0.02- 0.53, 0.01- 0.59, and 0.02- 0.37 µM against MGC-803, P15, and SW1990 cancer cells respectively.[48,49] Peruvoside, a cardiac glycoside from *Thevetia neriifolia* Juss. ex A. Dc. (Family *Apocynaceae*) was reported to induce selective inhibition of cell growth in androgen-sensitive and resistant prostate tumors by induction of apoptosis at 50nM as compared to other cardiac glycosides tested in the study.[50] Feng *et al.* [51] study showed the leukemic cell cycle arrest at the G2/M phase by peruvoside, thereby acting as an anti-blood cancer agent in the human primitive AML KG1a cells with a significant IC_{50} of 26 and 31 nM at 24 and 48 h respectively. The *in vitro* MTT colorimetric assay using several cancer cell lines showed that hellebrigenin has a significant growth inhibitory concentration of 10 nM, against U373 GBM cells.[52] The morphological analysis *via* the computer-assisted phase-contrast microscopy of the cell line during the 72 h treatment with hellebrigenin showed cell shrinkage, blebbing of the cell membrane, pyknotic bodies' formation as a result of the condensed chromatin as described in a previous study.[53]

Convallarin, a crystalline compound, isolated from the bulb of *Ornithogalum umbellatum* displayed a cytotoxic potential against Eagle's KB stain of epidemoid carcinoma with an ID_{50} of 0.002 y/mL.[54] Both the colorectal cancer cell lines SW480 and HCT116 were resistant to the anti-cancer effects of helveticoside using a cell viability assessment *via* Trypan blue exclusion and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays through a concentration and time-dependent cytotoxicity. Furthermore, the mechanism of action of the compound was evaluated by flow cytometry and membrane potential which led to the conclusion about helveticoside activity against the cancer cells through apoptosis.[55]

In a recent study by Ambali *et al.* [33], helveticoside isolated from *S. hispidus* DC exhibited significant cytotoxic activity against breast carcinoma cells, AU565 (CC_{50}= 11.42 ± 0.60 µM).[56] This was in relation to helveticoside isolated from *Descurainia sophia* (L.) Webb ex Prant (*Brassicaceae*), showing activity against human lung cancer cell, A549.[57]

To investigate the cytotoxic potential of strophanthidin, human cancer cells from the breast (MCF-7), lung (A549), and liver (HepG2) were used.[58] As evidenced by drug-induced DNA damage, the results show that strophanthidin was cytotoxic to MCF-7, A549, and HepG2 cells in a dose-dependent manner.[44]

Table 2: Medicinal plants that produce Cardenolides

Plant Family	Genera
Apocynaceae	*Nerium, Strophanthus, Apocynum, Adenium, Acokanthera, Carbera, Thevetia*
Asclepiadaceae	*Asclepias, Calotropis, Gomphocarpus, Pachycarpus, Xysmalobium*
Celastraceae	*Euonymus, Lophopetalum*
Cruciferae	*Erysimum, Cheiranthus*
Leguminosae	*Coronilla*
Moraceae	*Antiaris, Antiaropsis, Castilla, Maquira, Naucleopsis*
Scrophulariaceae	*Digitalis, Isoplexis*
Sterculiaceae	*Mansonia*
Tiliaceae	*Corchorus*

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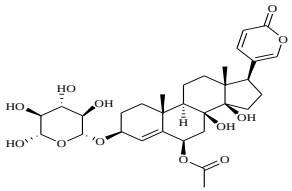
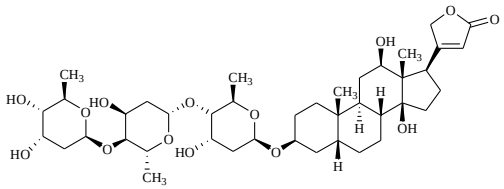
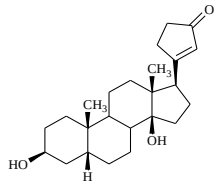


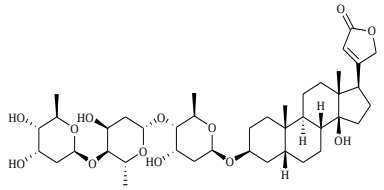
Scillirosidin



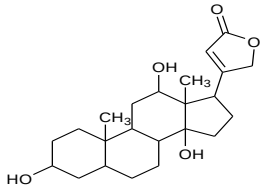
Digoxin



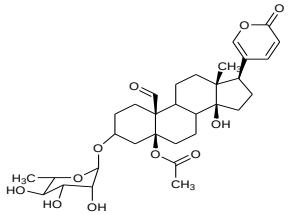
Digitoxigenin



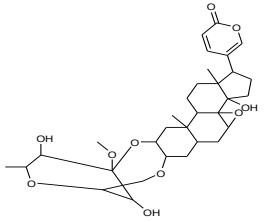
Digitoxin



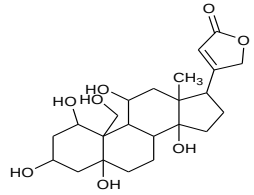
Digoxigenin



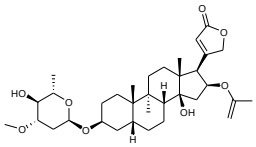
Lanceotoxin B



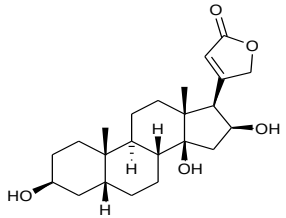
Cotyledoside



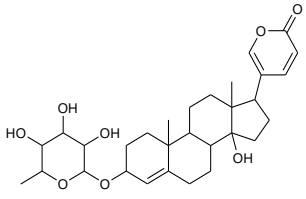
Ouabagenin



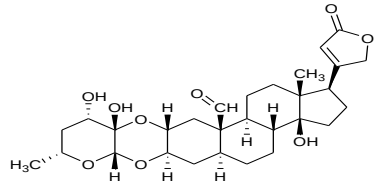
Oleandrin



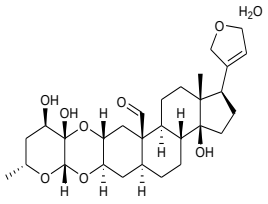
Gitoxigenin



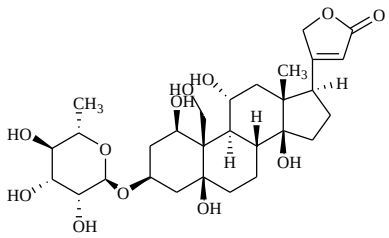
Proscillaridin A



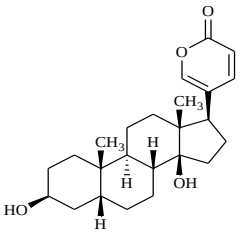
Calotropin



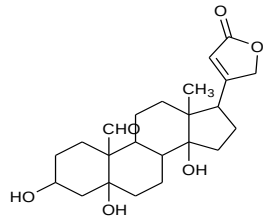
Calactin



Ouabain



Bufalin



Strophanthidin

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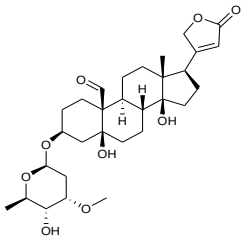
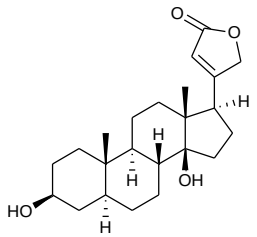
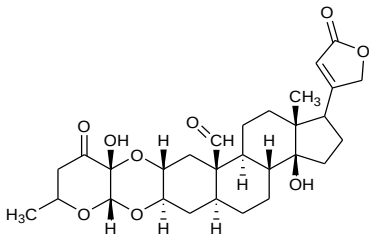


Cymarin



Uzarigenin



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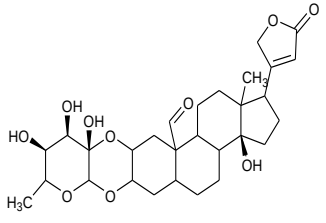

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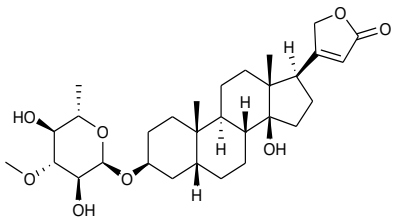
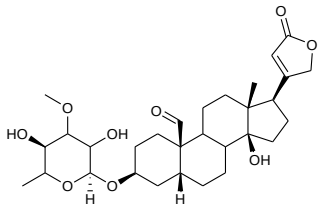
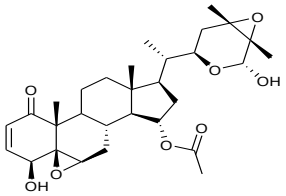


Neriifolin



Peruvoside



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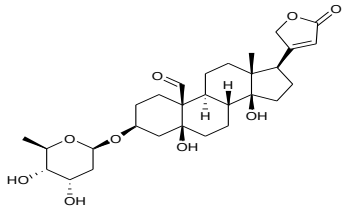

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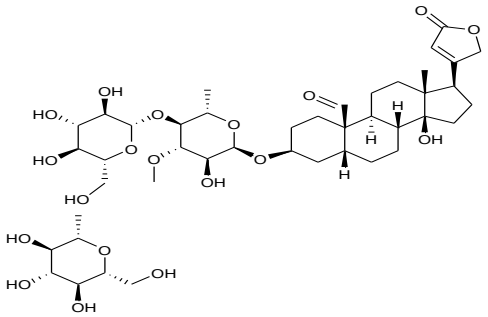
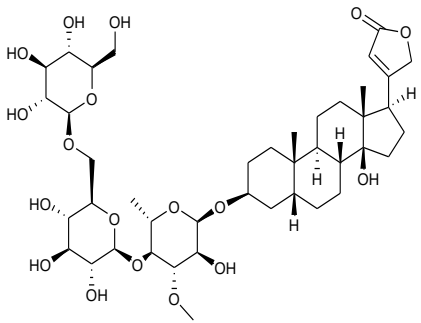


Thevetin A



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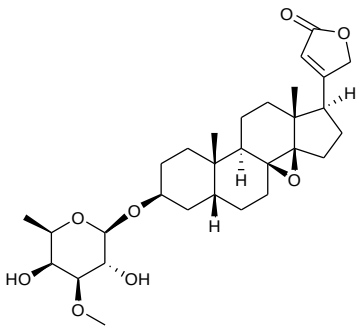
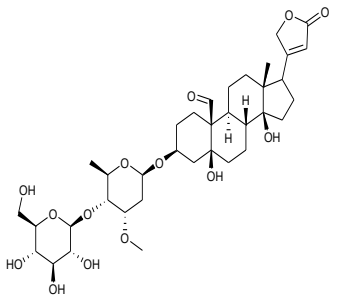


Cardenolide N-1



Strophanthin K

Figure 3: Chemical structures of selected cardiac glycosides

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Table 3: Pharmacological activities of cardiac glycosides from African medicinal plants

Plant name (family)	Compound name	Pharmacological/ Toxicological activities	References
Thevetia peruviana (Pers.) K. Schum. Apocynaceae	19-nor-neriifolin	Cytotoxicity	[49]
	19-nor-10-hydroxydigitoxigenin 3-O-α-L-thevetoside		
	Cannogenol 3-O-β-D-glucosyl-(1→4)-α-L-Thevetoside		
	Cannogenin 3-O-β-D-glucosyl- (1→4)-2′-O-acetyl-α -L-thevetoside		
	Digitoxigenin β-D-glucosyl-(l→4)-α-Lthevetoside		
	Neriifolin		
	Thevefoline		
	Ruvoside		
	Peruvoside		
	Thevetin B	-----	[69]
	Thevetin A		
	Acetylthevetin B		
	Acetylthevetin A		
	Thevetin C		
	Acethylthevetin C		
Thevetia neriifolia Juss. ex A. Dc. Apocynaceae	Peruvoside	Cytotoxicity (Anti-leukaemia) activity	[51]
		Cognitive function	[64]
		Anti-viral activity	[62]
Digitalis lanata Ehrh. Plantaginaceae	Digoxin	$NA^{+/}$ K^{+} ATPase inhibitory activity	[65, 66]
	Digitoxigenin		
	Digitoxin		
Tylecodon wallichii (Harv.) Toelken Crassulaceae	Cotyledoside	Toxic. Causes tremor	
Kalanchoe gracilis (L.) DC Crassulaceae	Bryophyllin B	Anti-viral activity	[63]
	lanceotoxin B	Neurotoxic ,	[70]
Nerium oleander L. Apocynaceae	Oleandrin , Oleander	Cytotoxic, Anti-inflammatory	[67]
	Cardenolide N-1	Anti-inflammatory	[71]
	Cardenolide N-2		
	Cardenolide N-3		[68]
	Cardenolide N-4, 3β,14-dihydroxy-5β,14β-card-20(22)-enolide		
	3β-O-(β,-D-diginosyl)-14-hydroxy-5β,14β-card-20(22)-enolide		

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	3β –O-(β-D-sarmentosyl)-16β-acetoxy-14-hydroxy- 5β,14β-card-20(22)-enolide		
	16β-acetoxy, 14-dihydroxy-5β,14β-card-20-(22)- enolide		
	3β,-O-(β-D-diginosyl)-16β,-acetoxy-14-hydroxy-5β,14β,-card-20(22)-enolide		
Securigera securidaca (L.) Degen&Dorfl. Fabaceae	Securidaside	-----	[72]
Convallaria majalis L. Lliliaceae	Convallerin, Convallamarin	Cardiotoxic	
Ornithogalum umbellatum L. Asparagaceae	Convallatoxin	Cytotoxicity	[54]
Erysimum cheirranthoides L. Brassicaceae	Helveticoside	Cytotoxicity	[55-57]
Descurainia sophia (L.) Webb ex Prant Brassicaceae, *Strophanthus hispidus* DC. Apocynaceae			
Strophanthus hispidus DC.	Strophanthin Ouabain	Cardiotoxic	

Strophanthidin decreased the expression of checkpoint and cyclin-dependent kinases in strophanthidin-induced cells, which further confirmed its influence on cell cycle arrest during the G2/M phase. Strophanthidin also inhibited the expression of multiple critical proteins, including mitogen-activated protein kinase (MEK1/ MAPK), Phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), mammalian Target of Rapamycin (mTOR), glycogen synthase kinase 3 (GSK3), and -catenin, through MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin. The outcome clearly shows how strophanthidin influences the expression of several critical proteins involved in cell cycle arrest, apoptosis, and autophagic cell death.[58]

To destroy cancer cells, cardiac glycosides may work in conjunction with anticancer medications. The identification of new anticancer candidates with potential action against both drug-sensitive and drug-resistant malignancies might thus be aided using cardiac glycosides as effective scaffolds.[59,60]

Recent data indicates that cardiac glycosides (CGs), as a result of efforts to discover novel therapeutic properties with desirable medicinal uses, may also be able to induce a broad spectrum of immunogenic cell death (ICD), a functionally unique type of apoptosis that initiates the proper immune responses.[61]

Antiviral Activity of Cardiac Glycosides Identified in African Medicinal Plants

Pharmacological potentials of cardiac glycoside; peruvoside was assayed against enterovirus and ribonucleic acid virus which are associated with several mammalian diseases such as poliomyelitis, meningitis, and encephalitis. Enterovirus A (EV-A71), belonging to the picornaviridae family served as a model for unraveling the mechanism of action of peruvoside in the management of some viral diseases such as the SARS-CoV-2. It was reported that viral RNA replication was inhibited by the cardiac glycoside, peruvoside thereby causing a reduction in the synthesis of viral protein thus leading to little or no disease occurrences.[62]

The anti-viral activities of bufadienolides isolated from *Kalanchoe gracilis* (L.) DC (*Crassulaceae*) showed that bryophyllin B prevented the Human Immunodeficiency Virus from replicating with an ED_{50} value of less than 0.25 μg/mL.[63]

Enzyme inhibitory activity of Cardiac glycosides Identified in African Medicinal Plants

Oral administration of peruvoside appeared to control cognitive heart failure in myocardial disease patients by having a substantial beneficial inotropic impact. At the onset of treatment with peruvoside, 2.4 mg was found to be an effective dose in the management and then with a subsequent dose of 0.6 mg for maintenance during a period of 15 weeks.[64]

Studies have shown the action of digitoxin and ouabain in inhibiting sodium-potassium pump (Na^+ K^+ ATPase). When cardiac glycosides attach to specific subunits, ATP binding is inhibited, which interferes with the enzyme's capacity to carry out this exchange effectively. As a result, cells are better able to absorb calcium, which in the case of failing cardiac myofibrils aids in producing a more effective myocardial contraction and enhances cardiac pump performance.[65] Ouabain, a cardiotonic is frequently used to treat a variety of cardiac problems, including heart failure, atrial fibrillation, and atrial flutters.[66]

Hellebrigenin had a significant Na^+/ K^+ ATPase inhibitory effect by the inhibition assay leading to an inhibition constant; of Ki 46 ± 6 nM, with a great affinity for the subunit α1β1 of the ATPase enzyme.[52]

Anti-inflammatory of Cardiac glycosides Identified in African Medicinal Plants

Oleandrin, a cardiac glycoside from *Nerium oleander* L. (*Apocynaceae*) served as an inhibitor during the activation of nuclear factor kappa B (NF-kB), which causes the innate immune system to produce proinflammatory cytokines including tumor necrosis factor-1, TNF- and interleukin-1, IL-1, thereby resulting in inflammation. This action is shown by inhibiting Ser536 phosphorylation or I kappaB kinase (IKK)-mediated phosphorylation prevents NF-kB activation. This in turn poses an anti-inflammatory response, as well as the prevention of tumor growth in the body.[67]

The intercellular adhesion molecule-1 (ICAM-1) was tested for inhibitory activity against induction in the *in vitro* anti-inflammatory activity of compounds isolated from *Nerium oleander*. ICAM-1 is an endothelial and leukocyte-associated transmembrane protein that aids leukocyte migration through endothelial cells by stabilizing cell-cell contacts. Cardenolide- N1 and 3β-O-(β,-D-diginosyl)-14-hydroxy-5β,14β-card-20(22)-enolide demonstrated considerable activity when IL-1 and TNF were present, with A549 cells, as a model for human endothelial cells.[68]

Conclusion

Cardiac glycosides are a huge class of secondary compounds produced by several natural processes and have a wide range of uses. Additionally, they share a chemical structure. Cardenolides and Bufadienolides are two different types of compounds found in cardiac glycosides, depending on how the aglycone's unsaturated lactone ring is arranged. Several medicinal plants in Africa are used to cure a variety of illnesses. Several cardiac glycoside metabolites have been previously isolated from these plants with promising pharmacological activities such as anti-viral, enzyme-inhibitory activity, anti-inflammatory, neurotoxic, cytotoxicity, and markers against coronary heart diseases which are considered non-communicable diseases. It is pertinent to note that the plant families *Apocynaceae* and *Asclepiadaceae* are the most abundant in Cardiac glycosides.

Despite the beneficial pharmacological activities of this class of secondary metabolites, toxicity has been reported in some of these compounds. Some of these chemicals' hazardous side effects might significantly restrict their therapeutic use in humans. Future research into how these cardiac glycosides' chemical structures might be altered to lessen their toxicity and improve their structural activity correlations may be worthwhile.

While reviewing articles on the pharmacological activities of cardiac glycosides, the authors observed there was little data on the isolation and characterization of cardiac glycosides from plants in West Africa and the world at large. The insufficient data availability on this metabolite could lead to the extinction of knowledge thereby not allowing biological assays on the secondary metabolite. Future research activities should therefore focus on the plants yet to be explored to possibly isolate more cardiac glycosides and other classes of compounds. The isolated compounds can therefore be screened for various biological activities.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Alsayegh AA, Abusudah WF, Almohmadi NH, Shaheen HM, Singh TG, De Waard M, Khan A. Assessment of Iris albicans lange as potential antimicrobial and analgesic agent. Molecules 2023; 18(1),e0280127. https://doi: 10.3390/molecules27217340 10.1371/journal.pone.0280127
2. Batiha GE, Akhtar N. Bioactive Compounds, Pharmacological Actions, and Pharmacokinetics of Genus Acacia 2022; 27(21). https://doi:10.3390/molecules27217340
3. Zhang X, Wang X, Zhang Y, Wang F, Zhang C, Li X. Development of isopentenyl phosphate kinases and their application in terpenoid biosynthesis. Biotechnol Adv 2023; 64. 108124. doi: a10.1016/j.biotechadv.2023.108124
4. Thirumurugan D, Cholarajan A, Raja S, Vijayakumar R. An Introductory Chapter: secondary metabolites. In book:

Secondary metabolites, sources, and Applications. 2018; https://doi: 10.5772/intechopen. 79766
5. Botelho AFM, Pierezan F, Soto-Blanco B, Melo MM. A review of cardiac glycosides: structure, toxicokinetics, clinical signs, diagnosis, and antineoplastic potential, Toxicon. 2018; https://doi.org/10.1016/j.toxicon. 11.429.
6. Prassas I, Diamandis EP. Novel therapeutic applications of cardiac glycosides. Nat Rev Drug Discov 2008; 7:926-935. https://doi: 10.1038/nrd2682.
7. Bhusare BP, John CK, Bhatt VP, Nikam TD. *In vitro* propagation of *Digitalis lanata* Ehrh. through direct shoot regeneration— A source of cardiotonic glycosides. Ind Crop Prod. 2018; 121:313–319. https://doi.org/10.1016/j.indcrop.2021114167.
8. Curfman G. Digitalis glycosides for heart rate control in atrial fibrillation. JAMA 2020; 324:2508.
9. Balderas-Lopez JL, Barbonetti S, Pineda-Rosas EL, Tavares-Carvalho JC, Navarrete A. Cardiac glycosides from *Cascabela thevetioides* by HPLC-MS analysis. Rev Bras Farmacogn 2019; 29:441–444. https://doi.org/10.1016/j.bjp.2019.04.008.
10. Qi J, Zulfiker AHM, Li C, Good D, Wei MQ. The Development of toad toxins as potential therapeutic agents. Toxins 2018; 10:336. https://doi: 10.3390/toxins10080336
11. Skubnik J, Pavlickova V, Rimpelova S. Cardiac Glycosides as Immune System Modulators. Biomolecules 2021; 11:659. https://doi.org/10.3390/biom11050659.
12. Ayogu JI, Odoh AS. Prospects and Therapeutic Applications of Cardiac Glycosides in Cancer Remediation. ACS Comb Sci, 2020; 22(11), 543-553. https://doi.org/ 10.1021/acscombsci.0c00082
13. El-Seedi, HR, Khalifa SAM, Taher EA, Farag MA, Saeed A, Gamal M, Efferth T. Cardenolides: Insights from chemical structure and pharmacological utility. Pharmacol Res, 2019; 141, 123-175. doi: 10.1016/j.phrs.2018.12.015
14. Riaz T, Akram M, Laila U, Zainab R, Khalil MT, Iftikhar M, Sfera A. Therapeutic applications of glycosides obtained from medicinal plants. Int Arch Int Med 2023; 10(8).
15. Boff L, Persich L, Brambila P, Ottoni FM, Munkert J, Ramos GS, Soares-Viana AR, Kreis W, Braga FC, Alves RJ. Investigation of the cytotoxic activity of two novel digitoxigenin analogues on H460 lung cancer cells. Anti-Cancer Drugs 2020; 31:452–462.
16. Ren Y, Wu S, Burdette JE, Cheng X, Kinghorn AD. Structural insights into the interactions of digoxin and Na+/K+-ATPase and other targets for the inhibition of cancer cell proliferation. Molecules, 2021; 26(12):3672.
17. Soto-Blanco B. Cardiac Glycosides Encyclopedia of Molecular Pharmacology 2022; (pp. 410-414): Springer.
18. Kreis W, Muller-Uri F. Biochemistry of sterols, cardiac glycosides, brassinosteroids, phytoecdysteroids, and steroid saponins, Annu Plant Rev. 2010; 40:304.
19. Kreis W. The foxgloves (*Digitalis*) revisited, Planta Med. 2017; 83:962. https://doi.org/10.1055/s-0043-111240.
20. Temilova SV, Kitashov AV, Nosov AM. Cardiac Glycosides: Distribution, Properties and Specificity of Formation in Plant Cell and Organ Cultures *in vitro*. Russian J Plant Physiol. 2022; 69:41. https://doi.org/10.1134/S1021443722030165.
21. Cuny E. Bioactive Ingredients of Helleborus niger L.(Christmas Rose): The Renaissance of an Old Medicinal Herb—A Review. Nat Prod Comm. 2023; 18(9):1934578X231201053.
22. Botelho AFM, Pierezan F, Soto-Blanco B, Melo MM. A review of cardiac glycosides: Structure, toxicokinetics, clinical signs, diagnosis and antineoplastic potential. Toxicon 2019; 158:63-68.
23. Tiamiyu AM, Okocha RC, Okunlade OA, Olatoye IO, Adedeji O. Phytochemical Constituents, Nutritional and Antibacterial Potentials of Selected Medicinal Plants 2023; 28(1):1-9. https://doi.org/10.22146/mot.78700.
24. Morsy N. Cardiac Glycosides in Medicinal Plants. Intech 2017 https://dx.doi.org/10.5772/65963.
25. Ekalu A, Ayo RGO, James HD, Hamisu I. A mini-review on the phytochemistry and biological activities of selected *Apocynaceae* plants. J Herbmed Pharmacol 2019; 8(4):269-273.
26. Sarkar AK. Emerging Trends of Bioscience Research 2019.
27. Saket K, Afshari JT, Saburi E, Yousefi M, Salari R. Therapeutic Aspects of Squill; An Evidence-Based Review. Curr Drug Discov Technol, 2020; 17(3):318-324. https://doi: 10.2174/1570163816666190125154745.
28. Steyn PS, van Heerden RF. Bufadienolides of plant and animal origin. Nat Prod Rep 1998; 15:397–413. https://doi:10.1039/A815397Y.
29. Khalaf H. Laboratory of Pharmacognosy College of Pharmacy, Al Bayan University Lab. 4 PART 1/ The chemical tests for cardioactive glycosides. Pharmacognosy Conference 2021.https://doi :10.13140/RG.2.2.12088.78084.
30. Mohammadhosseini M, Frezza C, Venditti A, Mahdavi B. An overview of the genus *Aloysia palau* (*Verbenaceae*): Essential oil composition, ethnobotany and biological activities. Nat Prod Res 2021 https://doi: org/10.108 0/14786419.2021.1907576.
31. Tyavambiza C, Dube P, Goboza M, Meyer S, Madiehe AM, Meyer M. Wound Healing Activities and Potential of Selected African Medicinal Plants and Their Synthesized Biogenic Nanoparticles. Plant (Basel), 2021; 10(12). https://doi: 10.1007/s11240-023-02485-8. 10.3390/plants10122635
32. Jeyasri R, Muthuramalingam P, Karthick K, Shin H, Choi SH, Ramesh M. Methyl jasmonate and salicylic acid as powerful elicitors for enhancing the production of secondary metabolites in medicinal plants: an updated review. Plant Cell Tissue Organ Cult 2023; 153(3):447-458. https://doi: 10.1007/s11240-023-02485-8.
33. Mohammadhosseini M, Venditti A, Sarker SD, Nahar L, Akbarzadeh A. The genus *Ferula*: Ethnobotany, phytochemistry, and bioactivities- a review. Ind Crop Prod. 2019; 129:350-394. https://doi.org/10.1016/j.indecrop.2018.12.012.
34. Akinwumi IA, Sonibare MA. *Sphenocentrum jollyanum* Pierre (*Menispermaceae*): From traditional medicine to pharmacological activity and chemical constituents. Trends Phytochem Res 2022; 6(4):301-313. https://doi: 10.30495/tpr.2022.1961991.1268.
35. Cock I, Mavuso N, Van Vuuren S. A Review of Plant-Based Therapies for the Treatment of Urinary Tract Infections in Traditional Southern African Medicine. Evidence- Based Compl Alter Med 2021; 7341124. https://doi:10.1155/2021/7341124.
36. Sitoe E, Van Wyk BE. An inventory and analysis of the medicinal plants of Mozambique. J Ethnopharmacol.2024;319(2): 117137.https://doi:10.1155/2021/7341124.
37. Oguntibeju OO. Medicinal plants with anti-inflammatory activities from selected countries and regions of Africa. J Inflamm Res. 2018; 11:307-317. https://doi: 10.2147/jir.s167789
38. Okaiyeto K, Oguntibeju OO. African Herbal Medicines: Adverse Effects and Cytotoxic Potentials with Different Therapeutic Applications. Int J Environ Res Public Health. 2021; 18(11). https://doi: 10.3390/ijerph18115988.
39. Mahomoodally MF. Traditional medicines in Africa: an appraisal of ten potent African medicinal plants. Evid-Based Complementary Altern Med. 2013; 1-14. https://doi.10.1155/2013/617459.
40. Fajinmi OO, Olarewaju OO, Staden JV. Traditional use of medicinal and aromatic plants in Africa. In book: Medicinal and Aromatic Plants of the World. 2017 Volume 3. https://doi: 10:1007/978-94-024-1120-1-3.
41. Heinrich M, Mah J, Amirkia V. Alkaloids Used as Medicines: Structural Phytochemistry Meets Biodiversity—

An Update and Forward Look. Molecules 2021; 26:1836. https://doi.org/10.3390/ molecules26071836.
42. Fouad YA, Aanei C. Revisiting the hallmarks of cancer. Am J Cancer Res. 2017; 7:1016–1036.
43. Kumavath R, Paul S, Pavithran H, Paul MK, Ghosh P, Barh D, Azevedo V. Emergence of Cardiac Glycosides as Potential Drugs: Current and Future Scope for Cancer Therapeutics. Biomolecules 2021; 11:1275. https://doi.org /10.3390/biom11091275.
44. Reddy D, Ghosh P, Kumavath R. Strophanthidin attenuates MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin signaling pathways in human cancers. Front Oncol 2020; 9:1469.
45. Reddy D, Kumavath R. Anticancer and Antiviral Properties of Cardiac Glycosides: A Review to Explore the Mechanism of Actions. Molecules 2020; 25(16). https://doi: 10.3390/molecules25163596
46. Al-Snafi AE. Bioactive ingredients and pharmacological effects of Nerium oleander. IOSR J Pharm 2020; 10(9):19-32.
47. Mekhail T, Kaur H, Ganapathi R, Budd GT, Elson P, Bukowski RM. Phase 1 trial of Anvirzel™ in patients with refractory solid tumors. Investigational new drugs, 2006; 24: 423-427.
48. Geng X, Wang F, Tian D, Huang L, Streator E, Zhu J, Kurihara H, He R, Yao X, Zhang Y. Cardiac glycosides inhibit cancer through Na/K-ATPase-dependent cell death induction. Biochem Pharmacol. 2020; 182:114226. https://doi: 10.1016/j.bcp2020.114226.
49. Tian DM, Cheng HY, Jiang MM, Shen WZ, Tang JS, Yao XS. Cardiac glycosides from the seeds of *Thevetia peruviana*. J Nat Prod. 2016; 79(1):38-50. https://doi: 10.1046/j.1365-3156.1999.00397.x.
50. Li H, Zhou H, Wang D, Qiu J, Zhou Y, Li X, Rosenfeld MG, Ding S, Fu XD. Versatile pathway-centric approach based on high-throughput sequencing to anticancer drug discovery. Proc Natl Acad Sci. 2012; 109(12):4609-4614. https://doi: 10.1073/pnas. 1200305109.
51. Feng Q, Leong WS, Liu L, Chan WI. Peruvoside, a cardiac glycoside, induces primitive myeloid leukemia cell death. Molecules 2016; 21(4):534.
52. Banuls MY, Katz A, Miklos W, Cimmino A, Tal DM, Ainbinder E, Zehl M, Urban E, Evidente A, Kopp B. Hellebrin and its aglycone form hellebrigenin display similar *in vitro* growth inhibitory effects in cancer cells and binding profiles to the alpha subunits of the Na+/K+ ATPase. Molecular cancer 2013; 12(1):1-14. https://doi.org/10.1186/1476-4598-12-33.
53. Brady HJ. Apoptosis methods and protocols. 2004 Springer Volume 282.
54. Kelly R, Daniels EG, Spaulding LB. Cytotoxicity of cardiac principles. J Med Chem 1965; 8(4):547-548. https://doi: 10.1021/jm00328a037.
55. An N, Sun Y, Ma L, Shi S, Zheng X, Feng W, Shan Z, Han Y, Zhao L, Wu H. Helveticoside Exhibited p53-dependent anticancer activity against colorectal cancer. Arch Med Res. 2020; 51(3):224-232. https://doi.org/10.1016/j.arcmed.2020.02007.
56. Ambali OA. Bioassay-led isolation of cytotoxic compounds from extracts of *Aframomum melegueta* (Roscoe) K. Schum. seeds and *Strophanthus hispidus* Dc. whole plant. 2021; http://hdl.handle.net/123456789/1267.
57. Kim BY, Lee J, Kim NS. Helveticoside is a biologically active component of the seed extract of *Descurainia sophia* and induces reciprocal gene regulation in A549 human lung cancer cells. BMC genomics 2015; 16(1):1-14. https://doi: 10.1186/s12864-015-1918-1.
58. Reddy D, Kumavath R, Barh D, Azevedo V, Ghosh P. Anticancer and antiviral properties of cardiac glycosides: A review to explore the mechanism of actions. Molecules 2020; 25:3596. https://doi:10.3390/molecules25163596.
59. Guerrero A, Herranz N, Sun B, Wagner V, Gallage S, Guiho R, Wolter K, Withers DJ, Gil J. Cardiac glycosides are broad-spectrum senolytics. Nat Metabol. 2019; 1(11):1074–1088. https://doi: 10.1038/s42255-019-0122-z.
60. Hou Y, Shang C, Meng T, Lou W. Anticancer potential of cardiac glycosides and steroid-azole hybrids. Steroids 2021:171. https://doi: 10.1016/j.steroids.2021.108852.
61. Ayogu JI, Odoh AS. Prospects and Therapeutic Applications of Cardiac Glycosides in Cancer Remediation. ACS Comb Sci 2020; 22:543–553. https://doi.org/10.1021/acscombsci.0c0082.
62. Wu KX, Yogarajah T, Loe MWC, Kaur P, Lee RCH, Mok CK, Wong YH, Phuektes P, Yeo LS, Chow VTK, Tan YW, Chu JJH. The host-targeting compound peruvoside has a broad-spectrum antiviral activity against positive-sense RNA viruses. Acta Pharm Sin B 2023; 13(5):2039-2055. https://doi.org/10.1016/j.apsb.2023.03.015.
63. Wu KX, Yogarajah T, Loe MWC, Kaur P, Lee RCH, Mok CK, Wong YH, Phuektes P, Wu PL, Hsu YL, Wu TS, Bastow KF, Lee KH. Kalanchosides A− C, New Cytotoxic Bufadienolides from the Aerial Parts of *Kalanchoe gracilis*. Org Lett. 2006; 8(23):5207-5210. https://doi: 10.1021/ol061873m. PMID: 17078679.
64. Bhatia M, Manchanda S, Roy SB. Haemodynamic studies with peruvoside in human congestive heart failure. Br Med J. 1970; 3(5725):740-743.
65. Shandell MA, Capatina AL, Lawrence SM, Brackenbury WJ, Lagos D. Inhibition of the Na+/K+-ATPase by cardiac glycosides suppresses expression of the IDO1 immune checkpoint in cancer cells by reducing STAT1 activation. J Biol Chem 2022; 298(3).
66. David MNV, Shetty M. Digoxin In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556025.
67. Manna SK, Sah NK, Newman RA, Cisneros A, Aggarwal BB. Oleandrin suppresses activation of nuclear transcription factor-kappaB, activator protein-1, and c-Jun NH2-terminal kinase. Cancer Res 2000; 60(14):3838-3847. PMID: 10919658.
68. Zhao M, Bai L, Wang L, Toki A, Hasegawa T, Kikuchi M, Abe M, Sakai J, Hasegawa R, Bai Y, Mitsui T, Ogura H, Kataoka T, Oka S, Tsushima H, Kiuchi M, Hirose K, Tomida A, Tsuruo T, Ando M. Bioactive cardenolides from the stems and twigs of *Nerium oleander*. J Nat Prod. 2007; 70(7):1098-103.https://doi: 10.1021/np068066g.
69. Kohls S, Scholz-Bottcher BM, Teske J, Zark P, Rullkotter J. Cardiac glycosides from Yellow Oleander (*Thevetia peruviana*) seeds. Phytochem. 2012; 75:114-127.
70. Henn D, Venter A, Botha C. *In vitro* cytotoxicity induced by the bufadienolides 1α, 2α-epoxyscillirosidine and lanceotoxin b on rat myocardial and mouse neuroblastoma cell lines. Toxins 2019; 11(1):14. https://doi: 10.3390/toxins11010014.
71. El-Seedi HR, Burman R, Mansour A, Turki Z, Boulos L, Gullbo J, Goransson U. The traditional medical uses and cytotoxic activities of sixty-one Egyptian plants: discovery of an active cardiac glycosides from *Urginea maritima*. J Ethnopharmacol. 2013; 145(3):746-757. https://doi: 10.1016/j.jep.2012.12.007.
72. Tofighi Z, Saeidi G, Hadjiakhoondi A, Yassa N. Determination of cardiac glycosides and total phenols in different generations of *Securigera securidaca* suspension culture. Res J Pharmacog. 2016; 3(2):25-31