Oleandrin: A cardiac glycosides with potent cytotoxicity

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ABSTRACT

Cardiac glycosides are used in the treatment of congestive heart failure and arrhythmia. Current trend shows use of some cardiac glycosides in the treatment of proliferative diseases, which includes cancer. *Nerium oleander* L. is an important Chinese folk medicine having well proven cardio protective and cytotoxic effect. Oleandrin (a toxic cardiac glycoside of *N. oleander* L.) inhibits the activity of nuclear factor kappa-light-chain-enhancer of activated B chain (NF-κB) in various cultured cell lines (U937, CaOV3, human epithelial cells and T cells) as well as it induces programmed cell death in PC3 cell line culture. The mechanism of action includes improved cellular export of fibroblast growth factor-2, induction of apoptosis through Fas gene expression in tumor cells, formation of superoxide radicals that cause tumor cell injury through mitochondrial disruption, inhibition of interleukin-8 that mediates tumorigenesis and induction of tumor cell autophagy. The present review focuses the applicability of oleandrin in cancer treatment and concerned future perspective in the area.

Key words: Cardiac glycosides, cytotoxicity, oleandrin

INTRODUCTION

Cardiac glycosides are used in the treatment of congestive heart failure (CHF) and cardiac arrhythmia. These glycosides are found as secondary metabolites in several plants and in some animals, such as the milkweed butterflies [Figure 1].[1] Their utility in CHF results from an increased cardiac output by increasing the force of contraction. By increasing intracellular calcium as described below, cardiac glycosides increase calcium induced calcium release and thus contraction.[2] Ouabain and digoxin are used as cardiac glycosides since ancient time. Digoxin from the foxglove plant is used clinically, whereas ouabain is used only experimentally due to its extremely high potency.[3] Basically, cardiac glycosides are of two types-cardenolides (C-23 steroids with methyl groups at C-10 and C-13 and a five member lact at C-17) and bufadienolide (term derives from the toad genus *Bufo* that contains bufadienolide glycosides, the suffix-adien-that refers to the two double bonds in the lactone ring and the ending-olide that denotes the lactone structure. Consequently, related structures with only one double bond are called bufadienolide).

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Cardiac glycosides are composed of two structural features: The sugar (glycoside) and the non-sugar (aglycone-steroid) moieties. The R group at the 17-position defines the class of cardiac glycoside. Two classes have been observed in nature - the cardenolides and the bufadienolides [Figure 2]. The cardenolides have an unsaturated butyrolactone ring while the bufadienolides have a-pyrone ring.

The cardiac glycosides occur mainly in plants from which the names have been derived. *Digitalis purpurea*, *Digitalis lanata*, *Strophanthus gratus* and *Strophanthus kombe* are the major sources of the cardiac glycosides. The term "genin" at the end refers to only the aglycone portion (without the sugar). Thus, the word digitoxin refers to an agent consisting of digitoxigenin (aglycone) and three sugar moieties. The aglycone portion of cardiac glycosides is more important than the glycone portion [Table 1].

Mechanism of action of cardiac glycosides

Normally, Na^+-K^+ pumps in the cardiac myocytes pump the potassium ions inside and sodium ions out. Cardiac glycosides inhibit this pump using by stabilizing it in the E_2-P transition state; so that sodium cannot be extruded and intracellular sodium concentration therefore increases. A 2nd membrane ion exchanger, i.e., Na^+/Ca^{2+} exchanger, Plants producing cardiac glycosides

Cardenolide type

i) Antiaris toxicaria
ii) Strophanthus- ouabain g/k/e-strophanthin
iii) Digitalis lanata and Digitalis purpurea
iv) Digxin, Digitoxin,
v) Nerium oleander - oleandrin
vi) Asclepias sp.

Bufadienolide type

i) Drimia maritima

Animals producing cardiac glycosides

Bufadienolide type

i) Areobufagin
ii) Bufotal
iii) Cinobufagin
iv) Marinobufagin
v) Proscillaridin

Cardinolides type

i) Acetyldigitoxin
ii) Acetyldigoxin
iii) Digitoxin
iv) Digoxin
v) Digitalis
vi) Lantoside C
vi) Deslantoside
vii) Metidigooxin
viii) Gitoformate

Figure 1: Plants and animal producing cardiac glycosides

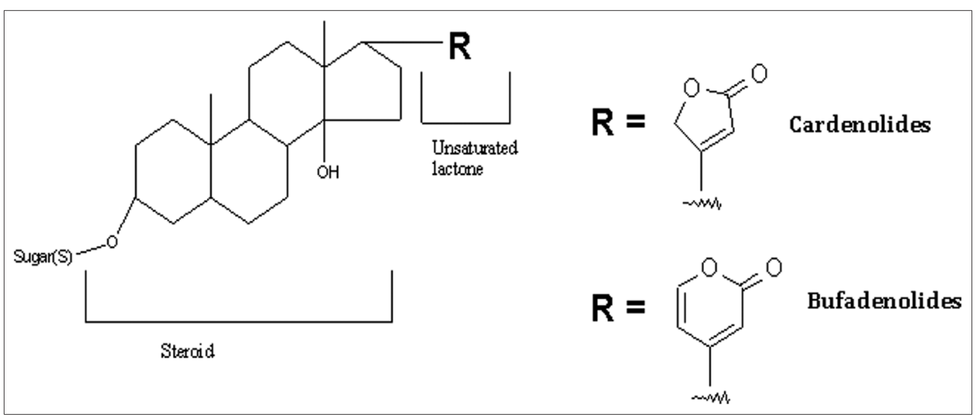
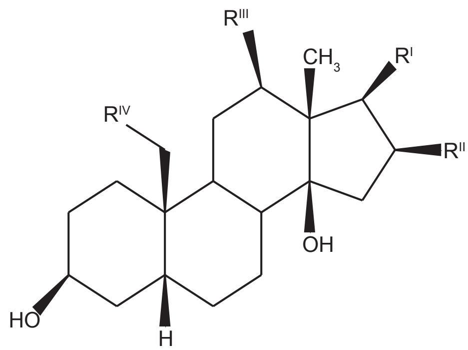


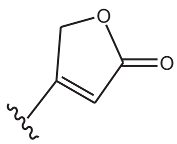
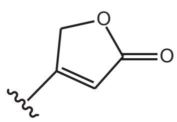
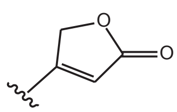
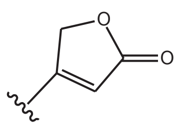
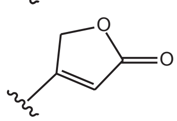
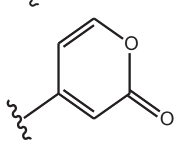
Figure 2: Generic structure of cardiac glycosides

is responsible for "pumping" calcium ions out of the cell and sodium ions in (3Na/Ca); raises intracellular sodium levels, which inhibit this pump; thus, calcium ions are not extruded and begins to build up inside the cell.[3] Increased cytoplasmic calcium concentrations cause increased calcium uptake into the sarcoplasmic reticulum (SR) through the sarco/endoplasmic reticulum Ca^{2+}-ATPase transporter.

Raised calcium stores in the SR allow for greater calcium release on stimulation so that myocytes could achieve faster and more powerful contraction by cross-bridge cycling [Figure 3]. The refractory period of the atrioventricular node is increased and finally cardiac glycosides function to regulate heart rate. Binding of cardiac glycoside to Na-K-ATPase is slow, but after binding, intracellular calcium increases gradually.[4] Thus, the action of cardiac glycosides is delayed. Raised extracellular K^+ decreases binding of cardiac glycoside to Na-K-ATPase. Consequently, increased toxicity of these drugs is observed in the presence of hypokalemia. If calcium of SR stores becomes too high, some ions are released

Table 1: Structure of some common cardiac glycosides



Name	R^{I}	R^{II}	R^{III}	R^{IV}
Digitoxigenin		H	H	H
Digoxigenin		H	OH	H
Gitoxigenin		OH	H	H
Ouabagenin		H	H	H
Strophanthidin		H	H	=O
Bufalin		H	H	H

spontaneously through SR receptors. After depolarization, this effect leads initially to bigeminy (regular ectopic beats following each ventricular contraction). If higher glycoside doses are given, rhythm is lost and ventricular tachycardia originates, followed by fibrillation.

Accumulating the *in vitro* and *in vivo* evidences highlighted the potential of anticancer properties of these compounds. Despite the fact that members of this family have advanced to clinical trial testing in cancer therapeutics, their cytotoxic mechanism is not yet elucidated [Tables 2a and b]. New findings within the past 5 years have revealed these compounds to be involved in complex cell-signal transduction mechanisms, resulting in selective control of human tumor, but not normal cellular proliferation. As such, they represent a promising form of cancer chemotherapy. New clinical studies of their anticancer potential as single or adjuvant treatments may provide insight into these potentially valuable therapeutic options.

Botanical description of *Nerium oleander* L. as source of oleandrin

A toxic cardiac glycoside isolated from *oleander* (*N. oleander* L.) is considered as important Chinese folk medicine [Figure 4]. *N. oleander* L is an evergreen shrub or small tree, family *Apocynaceae*. Toxicity is reported in all its part. *N. oleander* L is classified in the genus *Nerium*. It is most commonly known as *oleander*, from its superficial resemblance to the unrelated olive *Olea*. It is so widely cultivated that no precise region of origin has been identified, though Southwest Asia has been suggested. *Oleander* is one of the most poisonous of commonly grown garden plants.[28] *Oleander* grows to 2-6 m (6.6-20 feet) tall, with erect stems that splay outward as they mature; 1st year stems have a glaucous bloom while mature stems have a grayish bark.[29] The leaves are in pairs or whorls of three, thick and leathery, dark-green, narrow lanceolate, 5-21 cm (2.0-8.3 inches) long and 1-3.5 cm (0.39-1.4 inches) broad and with an entire margin. The flowers grow in clusters at the end of each branch; they are white, pink to red, 2.5-5 cm (0.98-2.0 inches) diameter, with a deeply 5-lobed fringed corolla round the central corolla tube. The fruit is a long narrow capsule 5-23 cm (2.0-9.1 inches) long, which splits open at maturity to release numerous downy seeds. *Oleander* grows well in warm subtropical regions, where it is extensively used as an ornamental plant in landscapes, in parks and along roadsides. *N. oleander* L is drought-tolerant and will tolerate occasional light frost down to − 10°C (14°F). Its toxicity renders it deer-resistant. It is tolerant of poor soils and drought. *Oleander* can also be grown in cooler climates in greenhouses and conservatories or as indoor plants that can be kept outside in the summer. *Oleander* flowers are showy and fragrant and are grown for these reasons. Over 400 cultivars have been named, with several additional flower colors not found in wild plants having been selected, including red, purple, pink and orange; white and a variety of pinks are the most common.

Oleandrin contains a central steroid nucleus with an unsaturated lactone structure on C-17 and a dideoxy arabinose group on C-3. In addition, the steroid ring has a substitute of an acetyloxy group on C-16. Oleandrigenin is derivative of oleandrin and this derivative is a more potent glycoside than ouabain.[30] *N. oleander* is classified in Table 3.

Oleandrin has structural similarity with other glycosides. Cardiac glycosides have more or less the same characteristics as oleandrin. Oleandrigenin is a deglycosylated metabolite of oleandrin. Physical properties of oleandrin are presented in Table 4.

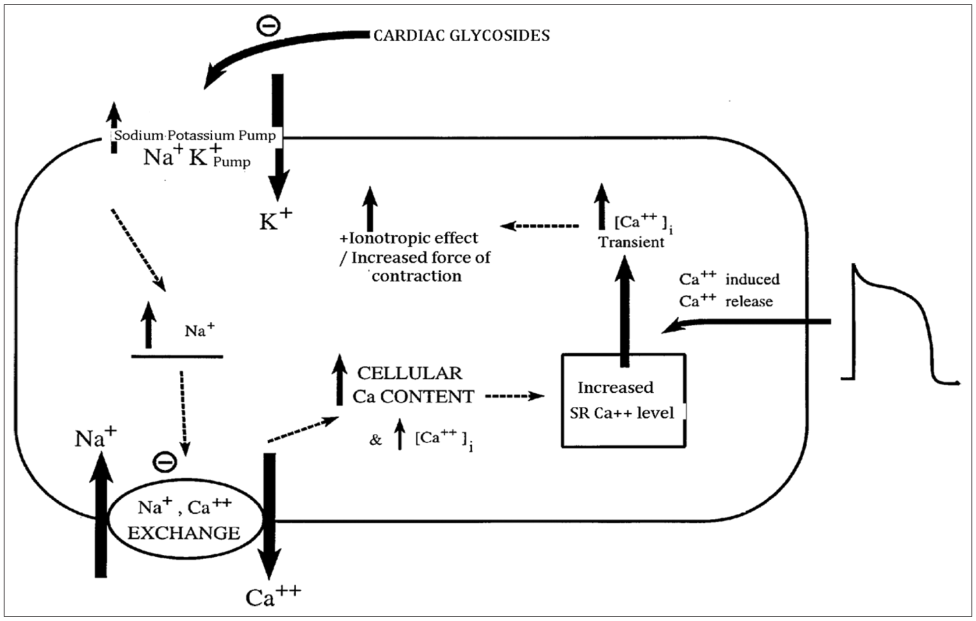


Figure 3: Mechanism of action of cardiac glycosides

Table 2a: Some important cytotoxic active cardiac glycosides

Cardiac glycosides	Plant/animal species	Cytotoxic effect reported on
Elaeodendrosides	Elaeodendron sp.	Human ovarian carcinoma (A2780)[5]
Acovenosigenin A 3-O-α-lramnopyranoside, Euonymoside A, Euonymusoside A	*Euonymus alata* (Thunb.) Sieb. (*Celastraceae*)	Human oral epidermoid (KB), promyelocytic lymphoma (HL-60), non-small-cell lung carcinoma (A549) and cervical carcinoma (Hela)[6]
Euonymoside A	*Euonymus sieboldianus* Blume (*Celastraceae*)	Human lung carcinoma (A549) and ovarian adenocarcinoma (SK-OV-3)[7]
Maquiroside A	*Maquira calophylla* (P. and E.) C.C. Berg (*Moraceae*)	Human oral epidermoid carcinoma (KB)[8]
Oleander, Oleandrin, Cardenolide N-1, cardenolide N-4, 3 β-O-(β-d-sarmentosyl)-16 β-acetoxy-14-hydroxy-5 β, 14 β-card-20-(22)-enolide, 16 β-acetoxy-3 β,14-dihydroxy-5 β, 14 β-card-20-(enolide)	*Nerium oleander* L. (*Apocynaceae*)	Human Jurkat leukemia (T-cell), HL (U-937), promyelocytic lymphoma (HL-60), cervical carcinoma (Hela), breast carcinoma (MCF-7), prostate carcinomas (LNCap, DU145, PC3), malignant fibroblast (VA-13), and liver carcinoma (HepG2)[9,10]
17-epi-11 α-hydroxy-6,7-dehydrostrophanthidin-3-O-β-boivinopyranoside; 6,7-dehydrostrophant hidin-3-O-β-boivinopyranoside; 6, 7-dehydrostro phanthidin-3-O-β-oleandropyranoside	*Nierembergia aristata* D. Don (*Solanaceae*)	Human breast carcinoma (BC1), fibrosarcoma (HT), lung cancer (LU1), melanoma (Mel2), colon carcinoma (Col2), oral epidermoid (KB), drug resistant KB with and without vinblastine, epidermoid carcinoma (A-431), prostate carcinoma (LNCaP), hormone dependent breast carcinoma (ZR-75-1) and glioma (U373)[11]
Convallatoxin	*Ornithogalum umbellatum* L. (*Hyacinthaceae*)	Human oral epidermoid carcinoma (KB)[12]
3′-O-β-d-glucopyranosylcalact in, 12-dehydroxyghalakinoside, 6′-dehydroxyghalakinoside, ghalakinoside, calactin	*Pergularia tomentosa* L. (Asclepiadaceae)	Kaposi's sarcoma[13]
Perilocin isomers	*Periploca graeca* L. (Asclepiadaceae)	Human prostate carcinoma (PC-3)[14]
Rhodexin A	*Rhodea japonica* (Thunb.) Roth. (*Liliaceae*)	Human leukemia (K562)[15]
Apocannoside, cymarin	*Apocynum cannabinum* L. (*Apocynaceae*)	Human nasopharynx carcinoma (KB)[16]
Calotropin, 16 α-acetoxycalotropin, 15 β-hydroxycalotropin, calactin, 15 β-hydroxycalactin, asclepin, 16 α-hydroxyasclepin, uscharidin	*Asclepias curassavica* (Asclepiadaceae)	Human lung carcinoma (A549), breast carcinomas (MCF-7 and MDA-MB-231) and hepatoma (HepG2)[17]

Contd...

Table 2a: Contd...

Cardiac glycosides	Plant/animal species	Cytotoxic effect reported on
Digitoxigenin, oleandrigenin, digitoxigenin, β-gentiobiosyl-α-l-cymaroside, Δ16-digitoxigenin β-d-glucosyl-α-l-cymaroside	*Beaumontia brevituba* Oliver (*Apocynaceae*)	Human breast carcinoma (BC1), colon carcinoma (Col2), fibrosarcoma (HT-1080), nasopharyngeal carcinoma (KB), vinblastine-resistant KB (KB-V1), lung carcinoma (Lu1) and melanoma (Mel2)[18]
Bufalin, cinobufagin	*Bufo bufo gargarizans* L.	Prostate carcinomas (LNCaP, DU145, PC3) and hepatoma (PLC/PRF/5)[19,20]
Calotropin, calactin, uscharin, voruscharin, 2-oxovoruscharin	*Calotropis procera* (Ait.) R. Br. (*Asclepiadaceae*)	Human non-small-cell lung carcinoma (A549), human glioblastomas (Hs683 and U373), human colon carcinomas (HCT-15 and LoVo), hepatoma (Huh7), non-hepatoma (COS-1) and colorectal carcinoma (COLO 320)[21,22]
2′-O-Acetyl cerleaside A, 17 α-neriifolin, 17 β-neriifolin, cerberin	*Cerbera odollam* Gaertner (*Apocynaceae*)	Human oral epidermoid carcinoma (KB), breast carcinoma (BC) and small-cell lung carcinoma (NCI-H187)[23]
Pyranoside	*Coronilla varia* L. (*Fabaceae*)	Human lymphocytic leukemia (P-388) and nasopharynx carcinomas (9KB)[24]
Securigenin-3 β-O-β-6-deoxyguloside, 19-hydroxy-sarmentogenin-3 β-O-β-6-deoxyguloside, sarmentogenin-3 β-O-(α -allosyl-(1→4)-β-6-deoxyalloside), securigenin-3 β-O-(α-allosyl-(1→4)-β-6 deoxyalloside)	*Crossopetalum gaumeri* (Loes.) Lundell (*Celastraceae*)	Human oral epidermoid carcinoma (KB)[25]
Digoxin, digitoxin, gitoxin	*Digitalis purpurea* L. (*Scrophulariaceae*) *Digitalis lanata* (*Scrophulariaceae*)	Human prostate carcinomas (LNCaP, DU145, PC3), renal adenocarcinoma (TK-10), breast adenocarcinoma (MCF-7), malignant melanoma (UACC-62) and chronic myelogenous leukemia (K-562)[26,27]

KB=Kappa-light-chain-enhancer of activated B chain, HL=Histiocytic lymphoma, MCF=Human breast adenocarcinoma cell line, NCI=small-cell lung cancer cell lines, LNCaP=Androgen-sensitive human prostateadenocarcinoma cells, HCT=Human colorectal carcinoma, PLC=Human hepatoma cell line, PRF=Alexander hepatoma cell line, TK=Human kidney adenocarcinoma cells, ZR=Human caucasian breast carcinoma cell line, BC=Breast cancer, PC=Prostate cancer

Figure 4: Flowers of *Nerium oleander* L

CHEMICAL CONSTITUENTS

Apart from cardiostimulatory action, *oleander* is diuretic also.[31] Cardenolides gentiobiosyl oleandrin and odoroside also are present in *Nerium*. The seeds contain glucosides (oleandrine, odorosides, adigoside). The bark contains glucosides (rosaginoside, nerioside, corteneroside). The roots of *Nerium* contain steroids.[32] Its lymph contains minerals[33] and α-tocopherol. There are also weakly active cardenolides (heterosides of uzarigenine) and inactive cardenolides (heteroside of adynergenine, of digitalose), triterpenoids, a resin, tannins, glucose, paraffin, ursolic acid, vitamin C are found in oleandrin. Some common structures are presented in Figure 5.

DOSAGE

Route of administration varies with type and location of disease.

- Parenteral: 0.3-0.7 ml intramuscular daily or every other day. Therapy continues until remission of disease. Doses up to 1.2 ml/m^2/d have been used in pharmacokinetic study
- Oral: 0.3-0.7 ml 3 times a day after meals (maximum of 2 ml per dose reported in patent)
- Gargle: 5% mouthwash used daily.

In a recent study, oleandrin, in Anvirzel™ has exhibited anti-cancer properties, but its efficacy against human immunodeficiency virus is still under investigation.[34] The principal active constituent of the botanical drug candidate PBI-05204, a supercritical CO_2 extract of *N. oleander* L, is the cardiac glycoside oleandrin and it exhibits potent anticancer activity as well as it is currently in phase I clinical trial as a treatment for patients with solid tumors.[35]

Oleandrin and oleandrigenin are able to inhibit proliferation

Table 2b: Structures of some important cytotoxic active cardiac glycosides

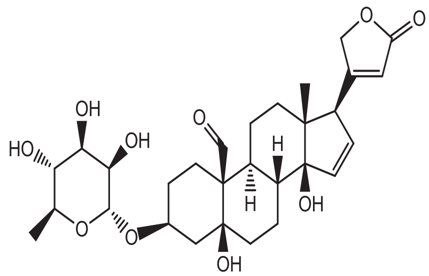
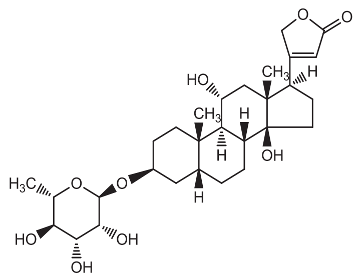
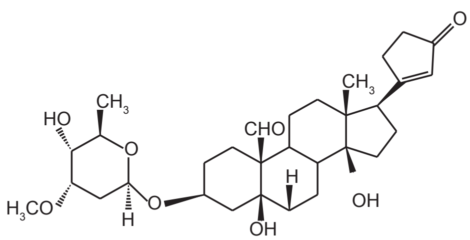
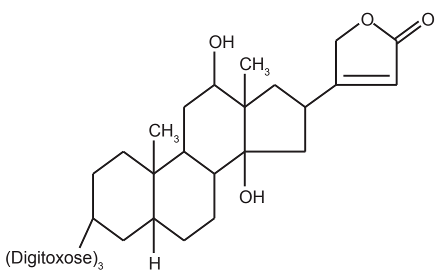
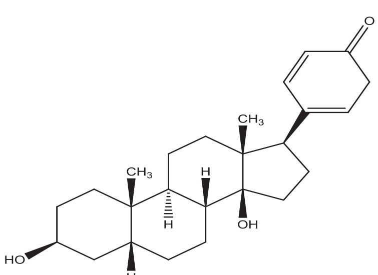
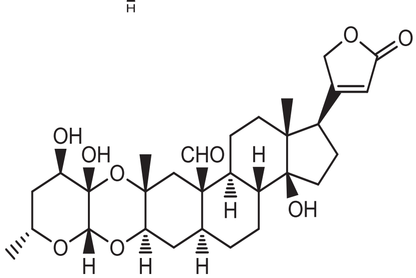
Cardiac glycosides	Structure
Convallatoxin	
Rhodexin A	
Cymarin	
Digoxin	
Bufalin	
Calotropin	

Table 3: Classification of *N. oleander*

Kingdom	Plantae (angiosperms)
(Unranked)	*Eudicots*
(Unranked)	*Asterids*
Order:	*Gentianales*
Family	*Apocynaceae*
Subfamily	Apocynoideae
Tribe	Wrightieae
Genus	*Nerium* L.
Species	*N. oleander*

N. oleander=Nerium oleander

Table 4: Physical properties of oleandrin

Properties	Detail
Molecular formula	$C_{32}H_{48}O_9$
Molar mass	576.72 g/mol
Appearance	Oleandrin forms colorless, odorless, acicular crystals that are very bitter
Melting point	250.0°C

of tumor cells and stimulate their apoptosis as a result of the high concentration of intracellular Ca^{++}. In addition, it inhibits the excretion of fibroblast growth factor-2 (FGF-2) through membrane interaction and through inhibition of the Na, K-ATPase pump.[36]

In PANC-1 cells (human pancreatic cancer cell line), cell death occurs not through apoptosis, but rather through autophagy and it has been noticed that oleandrin at low nanomolar concentrations potently inhibited cell proliferation associated with induction of a profound G(2)/M cell cycle arrest. Inhibition of cell cycle is not accompanied by any significant sub G1 accumulation of cells, suggesting a non-apoptotic mechanism of oleandrin.[37]

In a recent study, the effect of oleandrin on the growth of human and mouse cancer cells in relation to Na, K-ATPase subunits were investigated. oleandrin treatment resulted in selective inhibition of human cancer cell growth, but not rodent cell proliferation, which corresponded to the relative level of Na, K-ATPase alpha3 subunit protein expression. In a recent study, human pancreatic cancer cell lines has been observed for differentially expressing varying levels of alpha3 protein, but rodent cancer cells lacks discernable expression of this Na, K-ATPase isoform.[38]

Olendrin has shown to induce apoptosis in malignant cells through various *in vitro* tests on various cell lines, while human tumor cells are very sensitive to growth inhibition by oleandrin. Using human BRO and mouse B16 melanoma cell lines, several possible determinants of cell sensitivity to oleandrin and compared with ouabain were explored. This study included Na^+, K^+-ATPase activity and its isoforms as well as the cellular uptake of these cardiac glycosides. Oleandrin and ouabain induced apoptosis was detected in

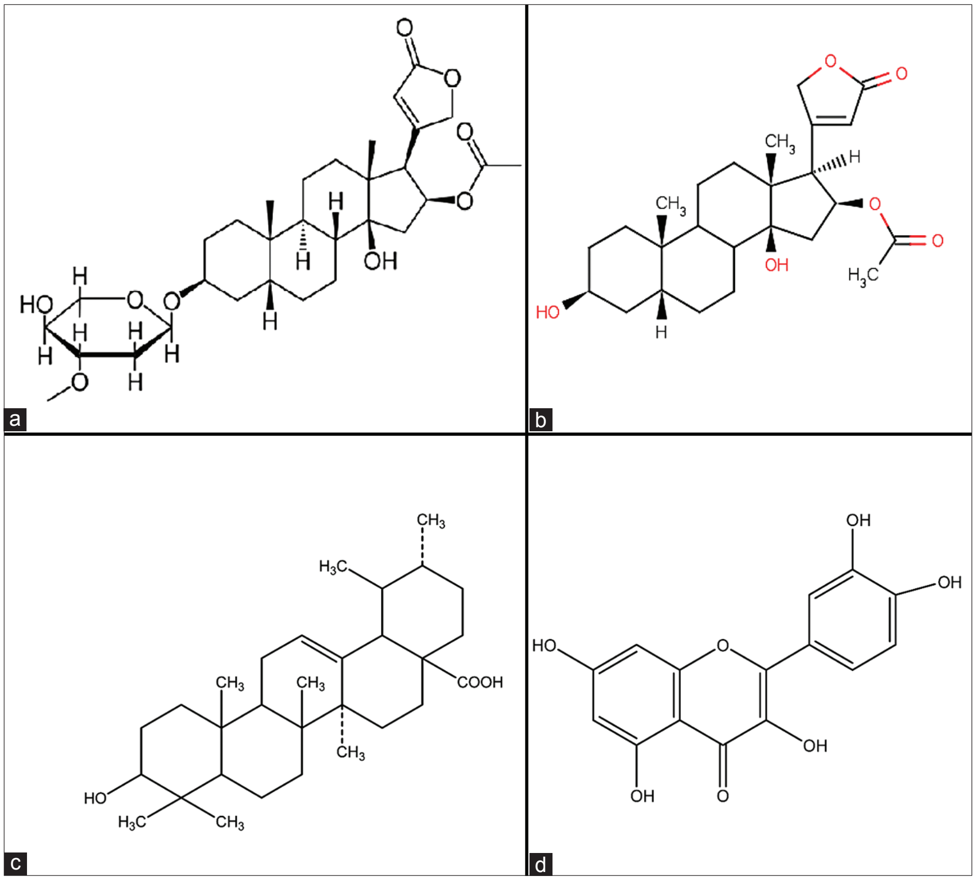


Figure 5: Structure of (a) oleandrin. (b) oleandrigenin. (c) ursolic acid. (d) quercetin

BRO cells while no evidence of cell death was observed in B16 cells even at concentrations 1000-fold higher than that used for BRO cells.[35]

Oleandrin poisoning by eating *oleander* leaves can be lethal at low dosages. Cases of sheep lethality have been reported to only one leaf of *oleander*. The symptoms present in poisoned animals include bloody diarrhea and colic, the latter especially in horses. Because the leaf itself is quite bitter, only starving animals will be likely to eat the plant. The lethal dosage for animals is estimated to be about 0.5 mg/kg.

PHARMACOKINETICS

Oleandrin has lipophilic property and it can be easily absorbed in the gastrointestinal tract after oral dosing. Oleandrin is metabolized into oleandrigenin in mice. Although oleandrigenin is not formed in human plasma, it was found in the volunteers injected with oleandrin, suggesting the fact that it is formed in other human tissues. The clearance is slow. Pharmacokinetic studies of (^{3}H) oleandrin, a cardiac glycoside component of Anvirzel™, were conducted in mice after either an intravenous (i.v.) dose (40 µg/kg) or a p.o. dose (80 µg/kg). Oleandrin was rapidly absorbed after oral dosing (C_{max} at 20 min) although the elimination half-life was longer (2.3 ± 0.5 h) than that after i.v. dosing (0.4 ± 0.1 h). The $AUC_{0-\infty}$ values obtained after i.v. and p.o. dosing were 24.6 ± 11.1 and 14.4 ± 4.3 (ng h/ml), respectively, resulting in an oral bioavailability of approximately 30%. After intra-venous administration of oleandrin in mice, the active metabolite is found to concentrate in the liver.[39]

It is excreted mostly in feces, but also in urine. Because the main route of excretion is through biliary excretion into the feces, it is mainly the liver that is exposed to oleandrin. As excretion in urine is only a smaller route, the kidneys are less exposed. There is also accumulation in the cardiac tissue, which explains its potential for cardiac toxicity. In mouse studies, it also appeared that oleandrin rapidly accumulates in brain tissue as it can pass through the blood-brain barrier. The data suggest that other components within *oleander* extract may enhance transport of oleandrin across the blood-brain barrier.[34]

ANTI-CANCER THERAPY AND MECHANISM OF ACTION

Oleandrin has potent anticancer activity and it is used for treatment of variety of cancers such as colon cancer, non-small cell lung cancer, leukemia, pancreas, melanoma and prostate.[37,40-44] As a cytotoxic agent, it generates reactive oxygen species and induces apoptosis. This may be due to its potential to inhibit P-glycoprotein. This transporter is responsible for phenotypes of cancer resistant to chemotherapeutic agents.[45] Apart from being a chemosensitizer, oleandrin has shown to be a potent radiosensitizer.[46] Oleandrin increases caspase activity in radiodamaged tumor cells and therefore, increases radiation-induced apoptosis. Mechanismically, oleandrin alteres the membrane fluidity, decreases activation of nuclear transcription factors NF-κB, jun N-terminal kinase and activation protein 1, increases intracellular calcium, increases expression of Fas ligand, increases reactive oxygen species production, oxidative injury and mitochondrial injury, decreases phosphorylation of Akt, Inhibits, the cellular transport of tumor growth factors (FGF-2), decreases the regulation of interleukin-8 receptors, initiates Apo2 ligand or tumor necrosis factor-related apoptosis-inducing ligand apoptosis through increased expression of death receptors four and five and activated the calcineurin and nuclear transcription factor nuclear factor of activated T-cells.[47-51]

CONCLUSION

Pharmacological activities of cardiac glycosides have increased significantly since the discovery of their effectiveness for treatment of CHF and also in proliferative disease. Development of clinically targeted, antiproliferative cardiac glycosides could be helped by systematic evaluations of several formulations and chemical variants in compound such as Oleandrtin (a lipid soluble cardiac glycoside). Further development of synthetic, semi-synthetic or naturally occurring cardiac glycosides, with assessment of their toxicity and structure-activity relationships, might expand the possibilities of finding a cardiac glycoside with a wider therapeutic index. Oleandrin, inhibits the proliferation of various cancer cells. Human melanoma and leukemia cells are more sensitive to oleandrin than murine tumor cells, normal human epithelial cells, peripheral blood mononuclear cells and neutrophils etc. Therefore, the role of oleandrin as antiproliferative agent cannot be ignored in cancer therapy.

REFERENCES

1. Vetter J. Plant cyanogenic glycosides. Toxicon 2000;38:11-36.
2. Schönfeld W, Weiland J, Lindig C, Masnyk M, Kabat MM, Kurek A, *et al*. The lead structure in cardiac glycosides is 5 beta, 14 beta-androstane-3 beta 14-diol. Naunyn Schmiedebergs Arch Pharmacol 1985;329:414-26.
3. Fameli N, van Breemen C, Kuo KH. A quantitative model for linking Na^+/Ca^{2+} exchanger to SERCA during refilling of the sarcoplasmic reticulum to sustain Ca^{2+} oscillations in vascular smooth muscle. Cell Calcium 2007;42:565-75.
4. Radzyukevich TL, Lingrel JB, Heiny JA. The cardiac glycoside binding site on the Na, K-ATPase alpha2 isoform plays a role in the dynamic regulation of active transport in skeletal muscle. Proc Natl Acad Sci U S A 2009;106:2565-70.
5. Cao S, Brodie PJ, Miller JS, Ratovoson F, Callmander MW, Randrianasolo S, *et al*. Antiproliferative cardenolides of an *Elaeodendron* sp. from the Madagascar rain forest (1). J Nat Prod 2007;70:1064-7.
6. Kitanaka S, Takido M, Mizoue K, Nakaike S. Cytotoxic cardenolides from woods of *Euonymus alata*. Chem Pharm Bull (Tokyo) 1996;44:615-7.
7. Baek NI, Lee YH, Park JD, Kim SI, Ahn BZ. Euonymoside A: A new cytotoxic cardenolide glycoside from the bark of *Euonymus sieboldianus*. Planta Med 1994;60:26-9.
8. Rovinski JM, Tewalt GL, Sneden AT. Maquiroside A, a new cytotoxic cardiac glycoside from *Maquira calophylla*. J Nat Prod 1987;50:211-6.
9. Zaboloshnaia ES. *Nerium oleander Apocynaceae* L. as a source of folinerin. Med Prom SSSR 1952;3:20-5.
10. Pathak S, Multani AS, Narayan S, Kumar V, Newman RA. Anvirzel, an extract of *Nerium oleander*, induces cell death in human but not murine cancer cells. Anticancer Drugs 2000;11:455-63.
11. Acosta MC, Moscone EA. B chromosomes in *Nierembergia aristata* (*Solanaceae*): Nucleolar activity and competition with the A chromosomes. Cytogenet Genome Res 2011;132:105-12.
12. Feinbrun N. The genus *Ornithogalum* in Palestine and neighbouring countries. Palest J Bot 1941;2:132-50.
13. Hamed AI, Plaza A, Balestrieri ML, Mahalel UA, Springuel IV, Oleszek W, *et al*. Cardenolide glycosides from *Pergularia tomentosa* and their proapoptotic activity in Kaposi's sarcoma cells. J Nat Prod 2006;69:1319-22.
14. Spera D, Siciliano T, De Tommasi N, Braca A, Vessières A. Antiproliferative cardenolides from *Periploca graeca*. Planta Med 2007;73:384-7.
15. Jung ME, Yoo D. First total synthesis of rhodexin A. Org Lett 2011;13:2698-701.
16. Johnson SA, Bruederle LP, Tomback DF. A mating system conundrum: Hybridization in *Apocynum* (*Apocynaceae*). Am J Bot 1998;85:1316-23.
17. Kupchan SM, Knox JR, Kelsey JE, Saenzrenauld JA. Calotropin, A Cytotoxic Principle Isolated From *Asclepias curassavica* L. Science 1964;146:1685-6.
18. Kaneda N, Chai H, Pezzuto JM, Kinghorn AD, Farnsworth NR, Tuchinda P, *et al*. Cytotoxic activity of cardenolides from *Beaumontia brevituba* stems. Planta Med 1992;58:429-31.
19. Yin XH, Li SN, Zhang L, Zhu GN, Zhuang HS. Evaluation of DNA damage in Chinese toad (*Bufo bufo gargarizans*) after *in vivo* exposure to sublethal concentrations of four herbicides using the comet assay. Ecotoxicology 2008;17:280-6.
20. Qi FH, Li AY, Lv H, Zhao L, Li JJ, Gao B, *et al*. Apoptosis-inducing effect of cinobufacini, *Bufo bufo gargarizans* cantor skin extract, on human hepatoma cell line BEL-7402. Drug Discov Ther 2008;2:339-43.
21. Soares de Oliveira J, Pereira Bezerra D, Teixeira de Freitas CD, Delano Barreto Marinho Filho J, Odorico de Moraes M, Pessoa C, *et al*. *In vitro* cytotoxicity against different human cancer cell lines of laticifer proteins of *Calotropis procera* (Ait.) R. Br. Toxicol *in vitro* 2007;21:1563-73.
22. Oliveira JS, Costa-Lotufo LV, Bezerra DP, Alencar NM, Marinho-Filho JD, Figueiredo IS, *et al*. *In vivo* growth inhibition of sarcoma 180 by latex proteins from *Calotropis procera*. Naunyn Schmiedebergs Arch Pharmacol 2010;382:139-49.
23. Wong SK, Lim YY, Abdullah NR, Nordin FJ. Assessment of antiproliferative and antiplasmodial activities of five selected *Apocynaceae* species. BMC Complement Altern Med 2011;11:3.

24. Williams M, Cassady JM. Potential antitumor agents: A cytotoxic cardenolide from *Coronilla varia* L. J Pharm Sci 1976;65:912-4.
25. Ankli A, Heilmann J, Heinrich M, Sticher O. Cytotoxic cardenolides and antibacterial terpenoids from *Crossopetalum gaumeri*. Phytochemistry 2000;54:531-7.
26. López-Lázaro M, Palma De La Peña N, Pastor N, Martín-Cordero C, Navarro E, Cortés F, *et al*. Anti-tumour activity of *Digitalis purpurea* L. subsp. heywoodii. Planta Med 2003;69:701-4.
27. Kroszczynski W. Recent achievements in the chemistry of *Digitalis lanata* and *Digitalis purpurea* glycosides. Biol Lat 1963;16:277-80.
28. LI CT, Deng SH, HO GB. Comparison of cardiotonic actions between oleandrin and digitoxin. Yao Xue Xue Bao 1964;11:540-4.
29. Yang P, Menter DG, Cartwright C, Chan D, Dixon S, Suraokar M, *et al*. Oleandrin-mediated inhibition of human tumor cell proliferation: Importance of Na, K-ATPase alpha subunits as drug targets. Mol Cancer Ther 2009;8:2319-28.
30. Hauck C, Potter T, Bartz M, Wittwer T, Wahlers T, Mehlhorn U, *et al*. Isoform specificity of cardiac glycosides binding to human Na^+, K^+-ATPase alpha1beta1, alpha2beta1 and alpha3beta1. Eur J Pharmacol 2009;622:7-14.
31. Siddiqui BS, Khatoon N, Begum S, Farooq AD, Qamar K, Bhatti HA, *et al*. Flavonoid and cardenolide glycosides and a pentacyclic triterpene from the leaves of *Nerium oleander* and evaluation of cytotoxicity. Phytochemistry 2012;77:238-44.
32. Turan N, Akgün-Dar K, Kuruca SE, Kiliçaslan-Ayna T, Seyhan VG, Atasever B, *et al*. Cytotoxic effects of leaf, stem and root extracts of *Nerium oleander* on leukemia cell lines and role of the p-glycoprotein in this effect. J Exp Ther Oncol 2006;6:31-8.
33. Abdolzadeh A, Shima K, Lambers H, Chiba K. Change in uptake, transport and accumulation of ions in *Nerium oleander* (rosebay) as affected by different nitrogen sources and salinity. Ann Bot 2008;102:735-46.
34. Ni D, Madden TL, Johansen M, Felix E, Ho DH, Newman RA. Murine pharmacokinetics and metabolism of oleandrin, a cytotoxic component of *Nerium oleander*. J Exp Ther Oncol 2002;2:278-85.
35. Lin Y, Dubinsky WP, Ho DH, Felix E, Newman RA. Determinants of human and mouse melanoma cell sensitivities to oleandrin. J Exp Ther Oncol 2008;7:195-20.
36. Shioda N, Fukunaga K. Functional roles of constitutively active calcineurin in delayed neuronal death after brain ischemia. Yakugaku Zasshi 2011;131:13-20.
37. Newman RA, Kondo Y, Yokoyama T, Dixon S, Cartwright C, Chan D, *et al*. Autophagic cell death of human pancreatic tumor cells mediated by oleandrin, a lipid-soluble cardiac glycoside. Integr Cancer Ther 2007;6:354-64.
38. Schoner W, Scheiner-Bobis G. Endogenous and exogenous cardiac glycosides: Their roles in hypertension, salt metabolism, and cell growth. Am J Physiol Cell Physiol 2007;293:C509-36.
39. Blum LM, Rieders F. Oleandrin distribution in a fatality from rectal and oral *Nerium oleander* extract administration. J Anal Toxicol 1987;11:219-21.
40. Davies RJ, Sandle GI, Thompson SM. Inhibition of the Na^+, K(+)-ATPase pump during induction of experimental colon cancer. Cancer Biochem Biophys 1991;12:81-94.
41. Mijatovic T, Roland I, Van Quaquebeke E, Nilsson B, Mathieu A, Van Vynckt F, *et al*. The alpha1 subunit of the sodium pump could represent a novel target to combat non-small cell lung cancers. J Pathol 2007;212:170-9.
42. Umebayashi C, Yamamoto N, Nakao H, Toi Y, Chikahisa-Muramatsu L, Kanemaru K, *et al*. Flow cytometric estimation of cytotoxic activity of rhodexin A isolated from *Rhodea japonica* in human leukemia K562 cells. Biol Pharm Bull 2003;26:627-30.
43. Newman RA, Yang P, Hittelman WN, Lu T, Ho DH, Ni D, *et al*. Oleandrin-mediated oxidative stress in human melanoma cells. J Exp Ther Oncol 2006;5:167-81.
44. Yeh JY, Huang WJ, Kan SF, Wang PS. Effects of bufalin and cinobufagin on the proliferation of androgen dependent and independent prostate cancer cells. Prostate 2003;54:112-24.
45. Garty H, Karlish SJ. Role of FXYD proteins in ion transport. Annu Rev Physiol 2006;68:431-59.
46. Verheye-Dua FA, Böhm L. Influence of apoptosis on the enhancement of radiotoxicity by ouabain. Strahlenther Onkol 2000;176:186-91.
47. Sreenivasan Y, Sarkar A, Manna SK. Oleandrin suppresses activation of nuclear transcription factor-kappa β and activator protein-1 and potentiates apoptosis induced by ceramide. Biochem Pharmacol 2012;22:205-18.
48. Svensson A, Azarbayjani F, Bäckman U, Matsumoto T, Christofferson R. Digoxin inhibits neuroblastoma tumor growth in mice. Anticancer Res 2005;25:207-12.
49. Manna SK, Sreenivasan Y, Sarkar A. Cardiac glycoside inhibits IL-8-induced biological responses by downregulating IL-8 receptors through altering membrane fluidity. J Cell Physiol 2006;207:195-207.
50. Almasan A, Ashkenazi A. Apo2L/TRAIL: Apoptosis signaling, biology, and potential for cancer therapy. Cytokine Growth Factor Rev 2003;14:337-48.
51. Ravi R, Bedi A. Sensitization of tumor cells to Apo2 ligand/TRAIL-induced apoptosis by inhibition of casein kinase II. Cancer Res 2002;62:4180-5.

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