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Cytotoxic Cardenolides from *Calotropis* Species: A Short Review

Eric Wei Chiang Chan[*1], Nuha I. Sweidan[2], Siu Kuin Wong[3] and Hung Tuck Chan[4]

[1]*Faculty of Applied Sciences, UCSI University, Cheras 56000, Kuala Lumpur, Malaysia*
[2]*Department of Chemistry, University of Petra, Amman 961343, Jordan*
[3]*School of Science, Monash University Sunway, Petaling Jaya 46150, Selangor, Malaysia*
[4]*Secretariat, International Society for Mangrove Ecosystems, c/o Faculty of Agriculture, University of the Ryukyus, Okinawa 903-0129, Japan*

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Abstract: From different plant parts of *Calotropis* species (*C. gigantea* and *C. procera*), various classes of compounds such as oxypregnanes, terpenoids, sterols, cardenolides and flavonoids have been isolated. Of these compounds, the cardenolides stand out as many of them have anticancer properties. Cardenolides are C_{23} steroids with a five-membered unsaturated butyrolactone ring consisting of a steroid nucleus, a lactone moiety at C-17 and a sugar moiety at C-3. The roles of cardenolides in the treatment of human cancer have been established as they can induce apoptosis and inhibit the growth of cancer cells. Structure–activity relationship analyses have yielded some interesting findings on their cytotoxicity. Compounds with six-membered ring sugar groups generally have significantly stronger inhibitory activity than those with five-membered ring sugar groups. A formyl or methyl-hydroxyl group at C-10 enhances cytotoxicity while the presence of a 4′-OH or 16-OH group decreases cytotoxicity. Chemical modification of 2”-oxovoruscharin, a novel cardenolide extracted from the root bark of *C. procera*, has led to the synthesis of UNBS1450. The compound is characterized by more potent anti-proliferative activity, lower toxicity, and is a strong sodium pump inhibitor and inducer of non-apoptotic cell death. UNBS1450 is currently in Phase I clinical trials.

Keywords: *Calotropis gigantea*; *Calotropis procera*; cytotoxicity; structure-activity relationship.

1. Introduction

Calotropis of the family Apocynaceae (Asclepiadaceae) is a small genus of three species with accepted names [1]. They are *Calotropis gigantea* (L.) Dryand. (syn. *Asclepias gigantea*), *Calotropis procera* (Aiton) Dryand. (syn. *Asclepias procera*) and *Calotropis acia* Buch. Ham. (syn. *Asclepias herbacea* and *Madorius acia*). These species are shrubs or small trees (3–4 m tall) with multiple stems and produce copious milky latex [2]. Leaves are opposite, thick, fleshy, broad and woolly underneath. Flowers are white and have five fleshy lobes with tips that are pale lilac in *C. gigantea* and purple violet in *C. procera* (Figure 1). Fruits are a fleshy aggregate with a pointed tip and seeds are ovoid with an apical tuft of white silky hairs. The two species are fast-growing and they flower throughout the year. Both *C. gigantea* and *C. procera* occur naturally from Africa to South and Southeast Asia including southern China while *C. acia* is restricted to India, Bangladesh and Nepal in South Asia [2].

[*] Corresponding author: E-Mail: erchan@yahoo.com; Phone: +603 9101 8880; Fax: +603 9102 3606.

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Figure 1. Flowers of *Calotropis gigantea* (left) and *Calotropis procera* (right).

From the many reviews on *Calotropis* species [3], *C. gigantea* [4–7] and *C. procera* [9–18], their uses in traditional medicine are so multifarious that all plant parts including the latex are remedy for many kinds of ailments and infections. A literature review on different plant parts of *C. procera* reported as many as 77 ethno-medicinal uses, notably, latex (27), leaves (19) and roots (10) [19]. The scientific evidence of some of these uses requires validation.

2. Phytochemistry

The chemical constituents of *C. gigantea* and *C. procera* have been extensively investigated, leading to the isolation of many oxypregnanes, terpenoids, sterols, cardenolides and flavonoids (Table 1). Of these classes of compounds, the cardenolides are outstanding in that many have anticancer properties by being cytotoxic to human cancer cells. Afroside, calactin, calotoxin, calotropagenin, calotropin, frugoside, 15β-hydroxycalactin, 12β-hydroxycoroglaucigenin, 15β-hydroxyuscharin, uscharidin, uscharin and uzarigenin are cardenolides reported in both species.

Table 1. Compounds reported in various plant parts of *Calotropis* species.

Compound class and name	Plant part	Reference
Calotropis gigantea		
Oxypregnanes		
Calotroposides A−G, S	Root, root bark	[20-23]
Calotropone	Root	[24]
Lignan derivatives		
Medioresinol	Leaf	[25]
Pinoresinol	Leaf	[25]
Terpenes/terpenoids		
β-Amyrin	Root	[20]
Anhydrosophoradiol-3-acetate	Flower	[26]
Drummondol	Leaf	[25]
Lupeol	Root	[20]
24-Methylenecycloartenol	Root	[20]
Taraxasterol	Root	[20]
Taraxasteryl acetate	Leaf	[25]
Sterols		
(24*R*)-24-Ethylcholest-4-en-3-one	Leaf	[27]
(24*S*)-24-Ethylcholest-4,22-dien-3-one	Leaf	[27]
6β-Hydroxy-24-ethylcholest-4,22-dien-3-one	Leaf	[27]
(24*R*)-3β-Hydroxy-24-ethylcholest-5-en-7-one	Leaf	[27]
β-Sitosterol	Root bark	[28]
Stigmasterol	Root bark	[28]
3,5,8-Trihydroxy-24-methylcholest-6,22-diene	Leaf	[27]
Cardenolides		
3′-*O*-Acetylfrugoside	Bark	[29]
Afroside	Latex, root bark	[30,31]
3′-*epi*-Afroside	Latex	[31]

Asclepin	Latex	[31]
3′-*O*-Benzoylfrugoside	Bark	[29]
Calactin	Leaf, latex, root bark	[25,30,31]
Calactinic acid	Leaf	[32]
Calactinic acid ethyl ester	Root bark	[30]
Calactinic acid methyl ester	Leaf, latex	[25,31]
Calotoxin	Leaf, fruit, latex, root bark	[30-31]
Calotropagenin	Leaf	[32]
Calotropin	Leaf, latex, root, root bark	[30-33]
19-Carboxylcalactinic acid methyl ester	Leaf	[25]
Coroglaucigenin	Leaf, root, root bark	[30-34]
19-deoxy-15β-Hydroxyuscharin	Latex	[31]
19-Dihydrocalactin	Root bark	[30]
4′-β,15β-Dihydroxycalactin	Root bark	[30]
18,20-Epoxycalotropin	Leaf	[25]
Frugoside	Leaf, fruit, latex, root, root bark	[30-34]
4′-β-D-Glucofrugoside	Root	[20]
4′-*O*-β-D-Glucopyranosylfrugoside	Root	[33]
Gofruside	Root	[24]
Gomphoside	Latex	[31]
3′-*epi*-Gomphoside	Latex	[31]
19-*nor*-10-Hydrocalactinic acid methyl ester	Leaf	[25]
15β-Hydroxycalactin	Latex, root bark	[30,31]
16α-Hydroxycalactin	Root bark	[30]
15β-Hydroxycalactinic acid ethyl ester	Root bark	[30]
15β-Hydroxycalactinic acid methyl ester	Root bark	[30]
16α-Hydroxycalactinic acid methyl ester	Leaf	[32]
15β-Hydroxycalotropin	Leaf, fruit, latex, root bark	[25,30,31]
16α-Hydroxycalotropin	Leaf, latex	[31,32]
16α-Hydroxycalotropagenin	Leaf	[32]
15β-Hydroxycardenolide	Leaf	[32]
12β-Hydroxycoroglaucigenin	Leaf	[32]
15β-Hydroxyuscharin	Latex, root bark	[30,31]
16β-Hydroxyuscharin	Latex	[31]
3′-*O*-Methylcalotropin	Bark	[29]
2′′-Oxovoruscharin	Latex	[31]
Uscharidin	Latex	[31]
Uscharin	Leaf, root bark, latex	[27,30,31,35]
2′-*epi*-Uscharin	Latex	[31,35]
Uzarigenin	Leaf	[25]
Flavonoids		
Isorhamnetin-3-*O*-glucopyranoside	Aerial part	[36]
Isorhamnetin-3-*O*-α-rhamnopyranosyl (1′′′ → 6′′)-β-glucopyranoside	Latex	[37]
Isorhamnetin-3-*O*-rutinoside	Aerial part	[36]
Miscellaneous		
Di-(2-ethylhexyl)phthalate	Flower	[26]
Calotropis procera		
Oxypregnanes		
Calotroposides H–N, S	Root bark	[38,39]
Terpenes/terpenoids		
α-Amyrin acetate	Root	[40]
Calotropenyl acetate	Flower, latex, aerial part	[41,42]
α-Calotropeol	Latex	[43]
β-Calotropeol	Latex	[43]
Calotropoleanyl ester	Root bark	[44]
Calotroprocerol A	Root bark	[45]
Calotroproceryl acetates A, B	Root bark	[45]
Calotroprocerone A	Root bark	[45]
Calotropfriedelenyl acetate	Root bark	[46]

Calotropterpenyl ester	Root bark	[46]
Calotropursenyl acetate	Root bark	[45,46]
1,2-Dihexadecanoyl-3-phosphatyl glycerol	Root	[47]
Dihydrophytoyl tetraglucoside	Root	[47]
3β,27-Dihydroxy-urs-18-en-13,28-olide	Latex	[48]
Lupeol	Latex	[47]
3-*epi*-Moreretenol	Latex	[47]
Multiflorenol	Latex	[48]
Phytyl iso-octyl ether	Root	[49]
Procerasesterterpenoyl triglucoside	Root	[49]
Proceroleanenols A, B	Root bark	[46]
Pseudotaraxasterol acetate	Root bark	[45]
Taraxasterol	Latex, root bark	[45,47]
Urs-19(29)-en-3-β-ol	Latex	[48]
Urs-19(29)-en-3-yl acetate	Latex	[48]
Sterols		
β-Sitosterol	Latex	[42,48]
β-Sitosterol glucoside	Aerial part, root	[42,49]
Stigmasterol	Latex, root bark	[45,48]
Cardenolides		
Afrogenin	Latex	[50]
Afroside	Latex	[51]
β-Anhydroepidigitoxigenin	Stem	[51]
β-Anhydroepidigitoxigenin-3β-*O*-glucopyranoside	Stem	[51]
Calactin	Latex, aerial part	[42,47,50]
Calactoprocin	Latex	[50]
Calotoxin	Latex, aerial part	[42,47,50]
Calotropagenin	Latex	[47]
Calotropin	Latex, root bark, aerial part	[42,47,52]
Deglucouzarin	Stem	[53]
19-Dihydrocalotropagenin	Latex, aerial part	[42]
Dihydrouscharin	Latex	[54]
Dihydrovoruscharin	Latex	[55]
Frugoside	Stem, root bark	[52,53]
15β-Hydroxycalactin	Latex	[50]
12β-Hydroxycoroglaucigenin	Latex	[50]
15β-Hydroxyuscharin	Latex	[50]
Ischaridin	Aerial part	[42]
Ischarin	Aerial part	[42]
2´´Oxovoruscharin	Root bark	[55]
Procegenins A, B	Latex	[50]
Proceraside A	Root bark	[52]
Procerocid	Latex	[47]
Syriogenin	Latex	[47]
Uscharidin	Latex	[47]
Uscharin	Latex, aerial part	[42,47,50,54]
Uzarigenin	Stem, latex, aerial part	[42,51,53,56]
Uzarigenone	Stem	[53]
Uzarin	Stem	[56]
Voruscharin	Latex	[47,54]
Flavonoids		
5-Hydroxy-3,7-dimethoxyflavone-4'-*O*-β-glucopyranoside	Stem	[51]
3´-*O*-Methyl quercetin-3-*O*-rutinoside	Aerial part	[42]
Miscellaneous		
Butanediol diglucuronoside	Root	[40]
Methyl resorcinyl triglycoside	Root	[40]
(*E*)-Octadec-7-enoic acid	Root bark	[45]

Cardenolides are C_{23} steroids consisting of an unsaturated five-membered lactone ring with a double bond, which is attached to a steroid nucleus at C-17 and a sugar moiety at C-3 (Figure 2) [57]. The biosynthetic pathway of cardenolides involves cholesterol → 20α-hydroxycholesterol → pregnenolone → progesterone → cardenolide [58]. They are a large group of compounds with considerable structural diversity and have long been used as drugs for treating congestive heart failures [59,60]. Recently, their roles in the treatment of cancer have been established as they can induce apoptosis and inhibit the growth of cancer cell lines. At low concentrations, cardenolides have cytoprotective effects by stimulating proliferation and inhibiting cell death in normal cells [59]. Phytochemical studies have revealed that cardenolides are involved in complex cell-signal transduction mechanisms, resulting in the selective control of human tumour but not the proliferation of normal cells [60]. Therefore, cardenolides are promising agents for targeted cancer chemotherapy.

Many genera of plants from the family Apocynaceae are known to contain cardenolides. Besides *Calotropis*, they are also distributed in *Apocynum*, *Cerbera*, *Nerium*, *Strophanthus* and *Thevetia* [61]. Almost 200 compounds of cardenolides have been isolated and identified from this family of which about 25% of them have been reported to possess anticancer activity.

3. Cytotoxicity of Cardenolides

3.1. Calotropis gigantea

Cardenolides isolated from the root bark of *C. gigantea* exhibited cytotoxic activity against A549 and HeLa human cancer cells [30]. Results of this study indicated the following structure–activity relationships:

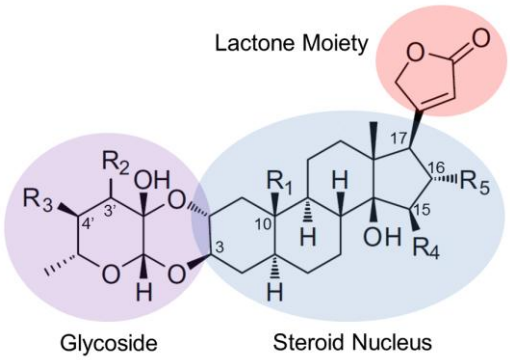
i) Compounds with six-membered ring sugar groups (Figure 2) showed significantly stronger inhibitory activity, notably, 19-dihydrocalactin (IC_{50} = 0.03 and 0.05 μM), calactin (IC_{50} = 0.02 and 0.03 μM), calotoxin (IC_{50} = 0.07 and 0.09 μM), and calotropin (IC_{50} = 0.03 and 0.05 μM). Compounds with five-membered ring sugar groups such as 15β-hydroxycalactinic acid methyl ester, 15β-hydroxycalactinic acid ethyl ester and calactinic acid ethyl ester were inactive (IC_{50} > 10 μM).

ii) A formyl (CHO) or methyl-hydroxyl (CH_2OH) group at C-10 enhanced cytotoxicity of the compounds. 15β-Hydroxycalactin with a CHO group was much more cytotoxic than afroside which has a CH_2 group. 19-Dihydrocalactin with a CH_2OH group displayed similar potency as calactin with a CHO group.

iii) The presence of 4'-OH or 16-OH groups decreased cytotoxicity. Calotoxin with an OH group at C-4' is three times less effective than calactin. 16α-Hydroxycalactin with an OH group at C-16 showed no cytotoxic activity.

Two new cardenolides along with 12 known compounds were isolated from the leaves of *C. gigantea* [25]. Seven of these compounds (18,20-epoxycalotropin, uzarigenin, calactin, calotropin, 15β-hydroxycalotropin, calactinic acid methyl ester and 19-carboxylcalactinic acid methyl ester) were evaluated for their cytotoxicity against KB, BC and NCI-H187 human cancer cell lines. Calactin was the most potent, whereas its 3′-epimer, calotropin was less potent, indicating the importance of the stereochemistry at C-3′. Uzarigenin, with no sugar unit and only a hydroxyl group at C-3, was much weaker than calotropin [25]. The IC_{50} values of calactin, calotropin and uzarigenin were 0.04, 0.06 and 9.61 μM against KB cells, 0.02, 0.04 and 8.95 μM against BC cells, and 0.35, 0.47 and 9.77 μM against NCI-H187 cells.

Among the cardenolides with similar sugar residues, the order of cytotoxic activity was calotropin > 15β-hydroxycalotropin > 18,20-epoxycalotropin, suggesting that the γ-lactone moiety is crucial for their cytotoxic activity [30]. The steric effect of the OH group at C-15 as in 15β-hydroxycalotropin reduced cytotoxicity. When comparing calotropin and calactinic acid methyl ester with six- and five-membered ring sugar moieties, respectively, calotropin was more cytotoxic. The presence of a formyl group at C-10 gave enhanced cytotoxic effect.



Cardenolide	R_1 (C-10)	R_2 (C-3′)	R_3 (C-4′)	R_4 (C-15)	R_5 (C-16)
Calactin	CHO	β-OH	H	H	H
Calotoxin	CHO	β-OH	OH	H	H
Calotropin	CHO	α-OH	H	H	H
19-Dihydrocalactin	CH_2OH	β-OH	H	H	H
15β-Hydroxycalactin	CHO	β-OH	H	OH	H
16α-Hydroxycalactin	CHO	β-OH	H	H	OH
15β-Hydroxycalotropin	CHO	α-OH	H	OH	H

Figure 2. Molecular structures of some cardenolides with six-membered ring sugar groups isolated from the root bark of *Calotropis gigantea* [30].

From the leaves of *C. gigantea*, 16α-hydroxycardenolide, calotropagenin, calotoxin, frugoside and 12β-hydroxycoroglaucigenin showed cytotoxic activity against KB, MCF7 and NCI-H187 human cancer cells [32]. Calotoxin displayed strong activity against KB cells while frugoside had good overall activity. KB cells were the most susceptible and MCF7 cells the least susceptible. Concurrently, uscharin isolated from the leaves of *C. gigantea* has been reported to exhibit potent cytotoxicity towards A549, HCT116 and HepG2 cancer cells with IC_{50} values of 0.003, 0.013 and 0.018 µg/mL, respectively [27].

From the roots of *C. gigantea*, coroglaucigenin, gofruside and frugoside showed cytotoxicity against K562 and SGC-7901 cancer cells [24,34]. IC_{50} values were 4.7 and 14 µg/mL for both coroglaucigenin and gofruside, and 3.4 and 6.5 µg/mL for frugoside. Coroglaucigenin with an OH group at C-3 was less active than frugoside, suggesting that a sugar unit at C-3 was crucial for the cytotoxic activity. Earlier, cardenolides from the roots of *C. gigantea* were tested for cytoxicity against a panel of cancer cell lines of human and mouse origin [33]. At 2 µg/mL, the compounds were cytotoxic to human cancer cells and not to mouse cancer cells. Against human cancer cells, calotropin exhibited the strongest activity followed by frugoside, 4'-*O*-β-D-glucopyranosyl frugoside and coroglaucigenin.

From the latex of *C. gigantea*, asclepin, calactin, calotropin, 15β-hydroxyuscharin, 19-deoxy-15β-hydroxyuscharin, gomphoside, 2′′-oxovoruscharin and uscharin were tested for their cytotoxic effects on MCF7 breast cancer cells [31]. All eight cardenolides demonstrated strong cytotoxicity with IC_{50} values ranging from 30.5 nM (asclepin) to 68.8 nM (gomphoside). They were not toxic to MCF10A normal breast cells (IC_{50} values > 20 µM).

3.2. Calotropis procera

The methanol, hexane, aqueous and ethyl acetate root extracts of *C. procera* were tested for cytotoxic activity against Hep2 cancer cells [62]. Results showed that the ethyl acetate root extract, known to be rich cardenolides, displayed the strongest cyctotoxic effect (96%) after 48 h of treatment compared to the extracts of methanol (73%) and hexane (61%). The extract treated Hep2 cells exhibited typical morphological changes of apoptosis through cell cycle arrest at the S phase which prevented the cells from entering the G2/M phase. This indicated that cardenolides in the extracts can inhibit the proliferation of Hep2 cells *via* apoptosis and cell cycle disruption. Similarly, the methanol

leaf extract *C. procera* has been shown to induce apoptosis and cell cycle arrest at G2/M phase in SK-MEL-2 cells human skin melanoma [63].

Out of four cardenolides isolated from the stems of *C. procera*, only uzarigenin (50 mM) was moderately cytotoxic towards human cancer cells of HT29 (59%) and HepG2 (35%) [50]. No inhibition of NIH-3T3 mouse fibroblast cells was observed. From the root bark of *C. procera*, proceraside A, frugoside and calotropin exhibited potent cytotoxic activity against A549, U373 and PC-3 cancer cells with IC_{50} values ranging from 0.01–0.30 μg/mL [51]. All three new cardenolides along with eight known ones isolated from the latex of *C. procera* displayed various degrees of cytotoxic activity [49]. Strongest activity was observed in calactin with IC_{50} values of 0.04 and 0.08 μM against A-549 and HeLa cells, respectively.

Chemical modification of 2´´-oxovoruscharin, a novel cardenolide isolated from the root bark of *C. procera*, has led to the synthesis of UNBS1450, a compound characterized by more potent anti-proliferative activity and lower toxicity [55,64,65]. The compound displayed anti-tumour activity against a panel of 57 human cancer cell lines that is comparable to taxol, and stronger than SN-38, two of the most potent drugs used in hospitals to treat cancer [55]. Against Hs683, U373, HCT-15, LoVo and A549, the IC_{50} values of UNBS1450 (3, 9, 24, 10 and 8 nM) were superior to those of 2”-oxovoruscharin (8, 15, 16, 10 and 74 nM), respectively.

UNBS1450 markedly inhibited the viability and proliferation of human prostate cancer cell but not of normal cells [66]. This non-apoptotic cancer cell death mediated by nucleolar targeting and down-regulation of c-Myc expression is a new mechanism of anti-tumour action. Through disorganization of the actin cytoskeleton, the compound possesses both anti-proliferative and anti-migratory properties [55,64,65]. UNBS1450 has shown to be a potent sodium pump inhibitor and induces non-apoptotic cell death. The compound induces apoptotic cell death in human leukemia cells at low concentrations [67]. It activates caspase-dependent apoptosis, suppresses the expression of Mcl-1, activating pro-apoptotic Bak and Bax proteins and eventually leading to cell death *via* the mitochondrial apoptotic pathway [67,68]. UNBS1450 is currently in Phase I clinical trials.

4. Non-cytotoxic Cardenolides

While most cardenolides isolated from *C. gigantea* and *C. procera* displayed cytotoxic activity against human cancer cells, there are reports that some did not have activity against certain cell lines. A compilation of cardenolides that are inactive against cancer cell lines tested are listed in Table 2 as a guide for researchers.

Table 2. Cardenolides of *Calotropis* species that are inactive against cancer cell lines tested.

Cardenolide	Plant part	Cancer cell line	Reference
Calotropis gigantea			
Afroside	Root bark	A549, HeLa	[30]
Calactinic acid ethyl ester	Root bark	A549, HeLa	[31]
19-Carboxylcalactinic acid methyl ester	Leaf	KB, BC, NCI-H187	[25]
Coroglaucigenin	Root	DLD-1, MKN-45, HepG2, Hu H7, PC-9, OST, LNCap	[33]
4’-β,15β-Dihydroxycalactin	Root bark	A549, HeLa	[30]
2α,15β-Dihydroxy-19-oxo-uzarigenin	Leaf	KB, MCF7, NCI-H187	[32]
16α-Hydroxycalactin	Root bark	A549, HeLa	[30]
15β-Hydroxycalactinic acid	Leaf	KB, MCF7, NCI-H187	[32]
15β-Hydroxycalactinic acid ethyl ester	Root bark	A549, HeLa	[30]
15β-Hydroxycalactinic acid methyl ester	Root bark	A549, HeLa	[30]
16α-Hydroxycalotropagenin	Leaf	KB, MCF7, NCI-H187	[32]
15β-Hydroxycalotropin	Root bark	A549, HeLa	[30]
Calotropis procera			
β-Anhydroepidigitoxigenin	Stem	HT29, HepG2	[51]
β-Anhydroepidigitoxigenin-3β-*O*-glucopyranoside	Stem	HT29, HepG2	[51]
2β,19-Epoxy-3β,14β-dihydroxy-19-methoxy-5α-card-20(22)enolide	Stem	HT29, HepG2	[51]

5. Cytotoxicity of Other Compounds

It is important to note that, besides cardenolides, other compounds of *C. gigantea* and *C. procera* such as oxypregnanes also exhibit cytotoxic activities. Calotroposides from the root bark of *C. gigantea* have also been reported to possess cytotoxic activity against cancer cell lines [22]. Calotropone from the roots of *C. gigantea* was cytotoxic towards K562 cells with IC_{50} value of 9.2 μg/mL [24]. From the root bark of *C. procera*, calotroposides K, M and S displayed the strong cytotoxic activity against A549, U373 and PC-3 cancer cells with IC_{50} values ranging from 0.5–4.4, 0.5–4.5 and 0.1–0.2 μM, respectively [38,39].

6. Conclusion

Although there are many reviews on *C. gigantea* and *C. procera*, this review is unique in that it focuses on the phytochemistry and cytotoxicity of cardenolides of these two species. Among the different classes of compounds isolated from *C. gigantea* and *C. procera*, the cardenolides are the most diverse and many have anticancer properties. Their roles in the treatment of human cancer have been established as they can induce apoptosis and inhibit the growth of cancer cells. In general, cardenolides with six-membered ring sugar groups have significantly stronger inhibitory activity than those with five-membered ring sugar groups. In this synopsis, a list of cardenolides from *C. gigantea* and *C. procera* that did not display any cytotoxic activity against certain cancer cell lines tested have been compiled as this information would serve as a useful guide for researchers. Chemical modification of 2′′-oxovoruscharin, a novel cardenolide isolated from the root bark of *C. procera*, has led to the synthesis of UNBS1450. The hemi-synthetic compound has more potent anti-proliferative activity, lower toxicity, and is a potent sodium pump inhibitor and inducer of non-apoptotic cell death. UNBS is currently in Phase I clinical trials. Besides cardenolides, other compounds of *C. gigantea* and *C. procera* such as oxypregnanes also exhibit cytotoxic activities.

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