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Review Article

Leveraging the cytotoxic attributes of Apocynaceae: current status and opportunities

Neamatullah W. A. Helmy[a], Ahmed M. Elissawy[a,b*], Nehal Ibrahim[b], Abdel Nasser B. Singab[a,b*]

[a]*Center of Drug Discovery Research and Development, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*

[b]*Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*

ABSTRACT

Plants of the Apocynaceae family have attracted more focus lately because of their capabilities as a source of cytotoxic lead compounds for cancer therapy. This review article presents a recent synthesis of the newest studies concerning the cell-damaging effects of plants in the Apocynaceae family, focusing on studies conducted between 2018 and 2023. The review covers the cytotoxic activity of various secondary metabolites isolated from different Apocynaceae plants, including *Catharanthus roseus*, *Melodinus cochinchinensis*, *Ervatamia pandacaqui*, and *Kopsia fruticosa*, among others. The cytotoxicity of various compounds derived from Apocynaceae plants has been tested on various cancerous cell types, such as those from breast, colon, and liver cancers, employing laboratory techniques like the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) and SRB (sulforhodamine B) assays to assess their effects. Additionally, this review sheds light on the mechanisms of cytotoxic action of the reported compounds, This includes triggering cell death and inhibition of cellular division, the review also emphasizes the importance of continued research into the cytotoxic properties of Apocynaceae plants and their potential applications in anticancer drug development. A careful evaluation of the potential toxicity on healthy cells and possible interactions with other chemotherapeutic agents is recommended.

Keywords: *Apocynaceae; Cytotoxicity; Secondary Metabolites; Catharanthus roseus; Melodinus cochinchinensis; Ervatamia pandacaqui and Kopsia fruticosa.*

***Correspondence** | Abdel Nasser B. Singab & Ahmed M. Elissawy; Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt. Email: dean@pharma.asu.edu.eg; aelissawy@pharma.asu.edu.eg

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1. Introduction

Cancer is a complex illness affected by both hereditary and external elements. Cancer is the second major cause of mortality worldwide with a rapidly increasing socioeconomic burden, The World Health Organization (WHO) states that breast and lung cancers are the leading causes of cancer deaths globally, with increasing incidences of colorectal, prostate, stomach, and liver cancers. There are various treatment options for cancer, including radiation therapy, medication, surgical procedures, and targeted local treatments, they often cause serious adverse reactions, toxic side effects, and secondary tumors **[1-3]**.

Chemotherapy is considered the backbone of treatment at various stages of many cancer types. However, it has several limitations and drawbacks that detrimentally affect its efficacy and safety. Some of the common side effects of chemotherapy include infections, easy bruising or bleeding, hair loss, nausea, vomiting, diarrhea, and fatigue. Chemotherapy may also harm

healthy cells, particularly the rapidly dividing ones like blood cells, cells in hair roots, and those in the gastrointestinal tract, Moreover, Chemotherapy treatments can be cost-prohibitive and not readily available for numerous patients, particularly in countries with lower economic resources. Furthermore, the emergence of chemotherapy resistance poses a significant challenge in treating cancer, underscoring the need for new cytotoxic compounds **[4-6]**. The advancement of formulation strategies, and the exploration of different drug combinations to face this growing challenge.

Plants and associated microorganisms are indispensable natural resources for discovering anticancer lead compounds with high structural and functional diversity, demonstrating various mechanisms of anticancer activity such as inducing apoptosis, inhibiting proliferation, metastasis, and angiogenesis, and modulating immune function **[1, 7]**.

The Apocynaceae family constitutes a significant group among the flowering plant categories, comprising 380 genera and 5,556 species of plants, many of which are known for their ornamental value and medicinal properties **[8]**. Lately, the cell-damaging capabilities of these plants have garnered increased fascination, particularly in the context of cancer therapy. A plethora of secondary metabolites have been isolated from Apocynaceae plants and many have displayed outstanding cytotoxic effects such as vinca alkaloids, camptothecin, and podophyllotoxins **[9]**` exhibiting diverse mechanisms of action, such as inhibition of microtubule assembly, topoisomerase I, and topoisomerase II, respectively **[9-11]**.

The review article intends to offer a current summary of recent studies on the toxic effects of Apocynaceae family plants. It focuses on the investigation of these plants' compounds and their potential to inhibit or kill cells, which is crucial for understanding their therapeutic applications and safety. The article likely covers various aspects such as ethnobotany, phytochemistry, and the biological activities of these plants, including their cytotoxic properties, focusing on studies conducted between 2018 and 2023. The research has been conducted on a variety of cancer cell types, including Caco-2 (colon cancer), MCF-7 (breast cancer), and HepG2 (liver cancer) cells with a brief discussion on reported mechanisms of action. To conduct this review, various online databases such as Google Scholar, PubMed, Egyptian Knowledge Bank (EKB), and chemical abstract search (sci-finder) have been explored using the keywords: Apocynaceae, plant, cytotoxicity, and anti-cancer.

2. Chemical review of the reported cytotoxic secondary metabolites isolated from different members of the family Apocynaceae.

2.1. Indole alkaloids

Six novel aspidofractinine alkaloids, namely, kopsiahainanins A-F **(1-6),** have been extracted from the branches and foliage of the *Kopsia hainanensis* plant. The cytotoxic activity of these alkaloids was assessed against seven human cancer cell lines (A-549, BGC-823, HepG2, HL-60, MCF-7, SMMC-7721, and W480). The most potent cytotoxic potential was observed for kopsiahainanins A and B **(1, 2)** with IC_{50} values ranging from 9.4-11.7 and 12.2-15.9 μM, respectively, while kopsiahainanins C demonstrated weak cytotoxicity against the tested cell lines (IC_{50}>20 μM) as illustrated in **Table (1) [12]**.

The study by Long et al conducted six new indole alkaloids isolated from *Kopsia fruticosa*, including kopsiafrutine A, B, C, D, E, and kopsifoline A **(7-12).** The compounds were tested for their ability to kill cancer cells across a range of cell lines, including skin, stomach, breast, and

colon cancers where kopsiafrutine C, D, and E **(13-15)** were effective against all the cell lines tested. Interestingly, Kopsiafrutine E (15) exhibited the strongest cytotoxic effect, with IC_{50} values (7.3, 8.6, 8.2, 9.5, 8.9, 8.6, and 9.2) µM on the cell lines HS-1, HS-4, SCL-1, A431, BGC-823, MCF-7, and W480, respectively. On the other hand, Kopsiafrutine C and D **(9, 10)** revealed promising activity against all tested cell lines with IC_{50} range of 11.8-13.8 µM and 10.3-12.5 µM, respectively. Meanwhile, kopsiafrutine A and B **(7, 8)** revealed moderate cytotoxic activity. Conversely, kopsifoline A **(12)** exhibited a relatively low cytotoxic activity against the dermatoma HS-4 and A431 cell lines and the colon cancer W480 cell line kopsifoline A with IC_{50} values of 67.3, 74.2, and 66.2 µM, respectively **[13]**.

A Chemical investigation of the aerial parts of *Tabernaemontana corymbosa* led to the isolation of nine new compounds and eight known ones: Taberyunine A-I **(13-21),** conophyllidine **(22),** conophylline **(23),** conofoline **(24),** tabernaelegantine B **(25),** 30-oxotabernaelegantine B **(26),** and taberdivarine C **(27),** F **(28),** and B **(29).** These compounds have attracted interest in various studies due to their potential biological activities **[14]**. For instance, A notable study by B.-J. Zhang et al. in 2018 evaluated the cytotoxicity of these alkaloids. The findings indicated that some of these alkaloids exhibited significant cytotoxic activity, while others did not. Specifically, Taberyunine A **(13)** displayed promising activity against three human cancer cell lines: HepG2, A549, and SGC7901 with IC_{50} values of 12.3, 16.8, and 9.8 µM, respectively. Conversely, other compounds, including Taberyunine E **(17)**, Taberyunine F **(18)**, Taberyunine G **(19)**, Taberyunine D **(16)**, confine **(24)**, and taberdivarine B (**29)** showed poor cytotoxicity with IC_{50} exceeding 40 µM. The cytotoxicity of these compounds is summarized in **Table 1 [14]**.

The investigation of the ethanolic extract from the leaves and twigs of *Ervatamia pandacaqui* resulted in the discovery of a novel monoterpenoid indole alkaloid, named 12-hydroxyakuamicine **(30).** This compound exhibited a moderate level of cytotoxicity towards the MCF-7 breast cancer cell line, with an IC_{50} value of 33.61 µM **[15]**.

In 2018, Zhou et al. uncovered three novel monoterpenoid bisindole alkaloids, along with thirteen previously identified compounds, extracted from the aerial segments of the plant *Tabernaemontana bufalina*. The newly identified alkaloids were characterized and named accordingly 3′-(2-oxopropyl)-19,20-dihydrotabernamine **(31)**, 3′-(2-oxopropyl)-ervahanine B **(32)**, and 19,20-dihydrovobparicine **(33),** and the known ones included isotabernamine **(34),** taberdivarine D **(35),** tabernaelegantine B **(36),** tabernaelegantinine B **(37),** 19,20-dihydrotabernamine A **(38),** taberdivarine E **(39),** ervadivaricatine B **(40),** taberdivarine F **(28),** tabernaecorymbosine A **(41),** tabernaelegantine C **(42),** tabernaelegantine A **(43),** conodurine **(44),** 19-(2-oxopropyl)-conodurine **(45)**. The isolated compounds were screened for their cytotoxicity against two human cancer cell lines, MCF-7 and A549 as detailed in **Table 1**. Notably, 3′-(2-oxopropyl)-19,20-dihydrotabernamine **(31)** showed significant cytotoxicity against MCF-7 and A549 cell lines with IC_{50} values of 3.07 and 4.78 µM, respectively **[16]**.

Pham and colleagues documented the extraction of nine distinct substances from *Catharanthus roseus* (L.) G. Don whole plant. These substances included a new monoterpenoid indole alkaloid, Catharoseumine **(46),** in addition to three new dimeric indole alkaloids named 17-deacetoxycyclovinblastine **(47),** 17-deacetoxyvinamidine **(48),** and 14’,15’-didehydrocyclovinblastine **(49),** together with

five known alkaloids were identified vinamidine **(50),** leurosine **(51),** catharine **(52),** cycloleurosine **(53),** and leurosidine **(54) [17]**. Catharoseumine **(46)** showed a moderate level of toxicity against HL-60 leukemia cells with an IC_{50} of 6.28 µM. Other dimeric indole alkaloids tested on MDA-MB-231 breast cancer cells exhibited strong effects, with IC_{50} values between 0.73 µM and 10.67 µM **[17]**.

A study performed by Zhan et al. on *Rauvolfia vomitoria* leaves reported the isolation and identification of rauvines B **(55),** a new yohimbine-type monoterpene indole alkaloid. Compound **55** revealed moderate cytotoxicity on MCF-7, SW480, and A549 cell lines with IC_{50} values of 25.5, 22.6, and 26 µM, respectively **[18]**.

The newly identified indole alkaloid named 5,6-dioxo-11-hydroxy voacangine **(56),** derived from the fruit of *Tabernaemontana contorta Stapf*, exhibited significant cytotoxic effects on the MDA-MB-231 breast cancer cell line, with an IC50 of 2.19 µM **[19]**.

Isovoacangine **(57)** and voacangine **(58)**, two alkaloids isolated from the root and leaf of *Tabernaemontana salzmannii*, were studied for their cytotoxic activity on human leukemia cells (THP-1) these studies revealed moderate to weak activity with IC_{50} value of 52.11 and 61.4 µM, respectively **[20]**.

In a study conducted by Abdul-Hameed et al, three new indole alkaloids, epirhazyaminine, 20-epi-sitsirikine, and burning (**59-61)** were isolated from the leaves of *Rhazya strict*, and their cytotoxic potential was evaluated on three cancer cell lines: HCT-116, PC-3, and HepG2. Weak cytotoxicity was recorded for **59-61** with IC_{50} range of 39-77, 76-85, and 45-72 µM, respectively. Interestingly, the isolated alkaloids displayed no cytotoxicity against the normal adult African green monkey kidney (VERO) cell line with IC_{50} >100 µM.

In addition to the previously mentioned compounds, four known indole alkaloids were isolated, namely, strictamine **(62)**, (16 R)-E-isositsirikine **(63),** antirhine **(64),** and strictanol **(65),** and they displayed weak cytotoxicity against the aforementioned cell lines, as detailed in **Table 1 [21]**.

Table 1: shows different IC_{50} values on different cell lines of the family Apocynaceae

cpd no	Class Type	Source	Cytotoxicity (IC_{50}) µM / Cell lines										Ref.
			gastric adenocarcinoma	skin cancer	leukemia	Breast cancer	prostate cancer	cervical cancer cell	Lung cancer	Fibroblast	colorectal cancer	hepatocellular carcinoma	
1.	aspidofractinine alkaloids,	*Kopsia hainanensis*	9.4 **BGC-823**		11.1 **HL-60**	10.4 **MCF-7**			11.3 3 **A-549**		11.7 **W480**	10.1 **HepG2**	**[11]**
2.			12.2 **BGC-823**		13.8 **HL-60**	14.3 **MCF-7**			12.7 **A-549**		15.9 **W480**	12.8 **HepG2**	
3.			31.2 **BGC-823**		32.2 **HL-60**	28.1 **MCF-7**			31.9 **A-549**		27.6 **W480**	30.7 **HepG2**	
4.			29.6 **BGC-823**		29.4 **HL-60**	27.1 **MCF-7**			29.7 **A-549**		24.9 **W480**	29.4 **HepG2**	
5.			68.7 **BGC-823**		72.3 **HL-60**	76.2 **MCF-7**			76.3 **A-549**		69.4 **W480**	66.8 **HepG2**	
6.			78.8 **BGC-823**		80.3 **HL-60**	80.5 **MCF-7**			80.2 **A-549**		81.8 **W480**	79.4 **HepG2**	
7.	alkaloid	Kopsia fruticosa	30.9 **BGC-823**	29.7 **A431**		27.1 **MCF-7**				28.1 **HS-4**			**[12]**
8.			35.5 **BGC-823**	30.1 **A431**		31.2 **MCF-7**				29.9 **HS-4**			
9.			12.3 **BGC-823**	11.8 **A431**		12.6 **MCF-7**				12.3 **HS-4**			
10.			11.7 **BGC-823**	10.3 **A431**		10.4 **MCF-7**				11.4 **HS-4**			
11.			8.9 **BGC-823**	9.5 **A431**		8.6 **MCF-7**				8.6 **HS-4**			

12.			–	74.2 **A431**	–		67.3 **HS-4**			
13.	indole alkaloid	*Tabernae montana corymbosa*	9.8 **SGC7901**			16.8 **A-549**		12.3 **HepG2**	**[13]**
14.	monoterpenoid alkaloids		0.7 **SGC7901**			2.1 **A-549**		1.5 **HepG2**	
15.			14.2 **SGC7901**			16.8 **A-549**		15.8 **HepG2**	
16.			>40 **SGC7901**			>40 **A-549**		>40 **HepG2**	
17.			>40 **SGC7901**			>40 **A-549**		>40 **HepG2**	
18.			>40 **SGC7901**			>40 **A-549**		>40 **HepG2**	
19.			>40 **SGC7901**			>40 **A-549**		>40 **HepG2**	
20.			2.4 **SGC7901**			5.1 **A-549**		3.5 **HepG2**	
21.			3.1 **SGC7901**			4.7 **A-549**		4.1 **HepG2**	
22.			0.87 **SGC7901**			1.15 **A-549**		0.8 **HepG2**	
23.			13.4 **SGC7901**			17.2 **A-549**		11.3 **HepG2**	
24.			>40 **SGC7901**			>40 **A-549**		>40 **HepG2**	
25.			2.8 **SGC7901**			4.6 **A-549**		3.1 **HepG2**	
26.			2.5 **SGC7901**			4.1 **A-549**		4.5 **HepG2**	
27.			2.4 **SGC7901**			6.1 **A-549**		3.5 **HepG2**	
28.									
29.			>40 **SGC7901**			>40 **A-549**		>40 **HepG2**	
30.	monoterpenoid indole alkaloids,	Ervatamia pandacaqui			33.61 **MCF-7**				**[14]**
31.	Monoterpenoid	*Tabernae montana bufalina*			3.07 **MCF-7**	4.78 **A-549**			**[13],[14]**
32.	Bisindole Alkaloids				2.15 **MCF-7**	4.15 **A-549**			
33.					3.63 **MCF-7**	2.52 **A-549**			
34.					1.38 **MCF-7**	2.12 **A-549**			
35.					13.97 **MCF-7**	37.95 **A-549**			
36.					3.41 **MCF-7**	10.08 **A-549**			
37.					3.73 **MCF-7**	3.72 **A-549**			
38.					5.37 **MCF-7**	31.72 **A-549**			
39.					1.25 **MCF-7**	1.19 **A-549**			
40.					3.4 **MCF-7**	3.38 **A-549**			
41.					1.44 **MCF-7**	4.24 **A-549**			
42.					10.87 **MCF-7**	14.53 **A-549**			
43.					12.95 **MCF-7**	23.82 **A-549**			
44.					3.91 **MCF-7**	5.42 **A-549**			
45.					6.13 **MCF-7**	5.19 **A-549**			
46.	new monoterpenoid indole alkaloids	Catharanthus roseus (L.) G. Don:		6.28 **HL-60**					
47.	dimeric indole alkaloids				range of 0.73–10.67 **MDA-MB-231**				**[16]**
48.									

49.													
50.	indole alkaloids												
51.													
52.													
53.													
54.													
55.	monoterpene indole alkaloids	*Rauvolfia vomitoria*			>40 **HL-60**	25.5 **MCF-7**			26.0 **A-549**	22.6 **W480**	>40 **SMMC-7721**	**[17]**
56.	indole alkaloid monoterpenoid alkaloids	*Tabernaemontana contorta Stapf*				3.35(24hr), 2.19(48hr) **MDA-MB 231**						**[18]**
57.	alkaloids	*Tabernaemontana salzmannii*		11.73 **A375**	52.11 **(THP-1)**							**[19]**
58.					61.40 **(THP-1)**								
59.	alkaloids	*Rhazya stricta*				40.5 **MCF-7**	39.0 **PC-3**	23.4 **HeLa**		45.0 **HCT116**	77.0 **HepG2**	**[20],[22]**
60.						52.2 **MCF-7**	76.0 **PC-3**	12.4 **HeLa**		81.0 **HCT116**	85.0 **HepG2**	
61.						50.7 **MCF-7**	62.0 **PC-3**	55.7 **HeLa**		45.0 **HCT116**	72.0 **HepG2**	
62.							82.0 **PC-3**			85.0 **HCT116**	87.0 **HepG2**	
63.							87.0 **PC-3**			85.0 **HCT116**	98.0 **HepG2**	
64.							71.0 **PC-3**			84.0 **HCT116**	90.0 **HepG2**	
65.							70.0 **PC-3**			69.0 **HCT116**	84.0 **HepG2**	
66.	bisindole alkaloids.	*Melodinus cochinchinensis*			5.2 **MOLT-4**							**[21]**
67.					1.5 **MOLT-4**								
68.	new monoterpene indole alkaloids	*Rhazya stricta*				68.9 **MCF-7**		30.7 **HeLa**			52.7 **HepG2**	**[22]**
69.						5.1 **MCF-7**		3.1 **HeLa**			5.1 **HepG2**	
70.	monoterpene indole alkaloids					93.2 **MCF-7**		36.9 **HeLa**			118.8 **HepG2**	
71.						65.4 **MCF-7**		23.2 **HeLa**			60.7 **HepG2**	
72.						50.0 **MCF-7**		32.8 **HeLa**			54.9 **HepG2**	
73.	monoterpenoid indole alkaloids	*Tabernaemontana bovina*		50.8 **SK-Mel-2**		52.4 **MCF-7**	42.9 **LNCaP**		66.3 **SK-LU-1**		60.8 **HepG2**	**[23]**
74.				> 100 **SK-Mel-2**		77.6 **MCF-7**	93.3 **LNCaP**		85.6 **SK-LU-1**		> 100 **HepG2**	
75.				> 100 **SK-Mel-2**		71.5 **MCF-7**	89.7 **LNCaP**		72.1 **SK-LU-1**		> 100 **HepG2**	
76.				> 100 **SK-Mel-2**		79.2 **MCF-7**	82.5 **LNCaP**		78.7 **SK-LU-1**		> 100 **HepG2**	
77.				59.1 **SK-Mel-2**		65.2 **MCF-7**	62.1 **LNCaP**		60.8 **SK-LU-1**		62.3 **HepG2**	
78.				> 100 **SK-Mel-2**		51.6 **MCF-7**	76.0 **LNCaP**		54.4 **SK-LU-1**		> 100 **HepG2**	
83.	monoterpenoid		20.6 **AGS**						15.1 **A-549**	12.0 **HCT116**	13.7 **HepG2**	**[24]**
84.	indole alkaloid dimers (MIADs),	*Melodinus axillaris*	11.7 **AGS**						11.2 **A-549**	15.7 **HCT116**	15.4 **HepG2**	
85.			15.6 **AGS**						10.3 **A-549**	5.3 **HCT116**	6.9 **HepG2**	
86.			12.7 **AGS**						7.7 **A-549**	3.9 **HCT116**	18.9 **HepG2**	
87.	Cardiac glycosides	*Strophanthus*	0.83 **SGC-7901**		0.38 **K562**			0.20 **HeLa**	2.07 **A-549**			**[26]**

88.		*divaricat us*	2.87 **SGC-7901**	1.49 **K562**	6.09 **HeLa**	3.16 **A-549**			
89.			0.57 **SGC-7901**	1.28 **K562**	0.66 **HeLa**	1.65 **A-549**			
90.			23.13 **SGC-7901**	5.18 **K562**	5.06 **HeLa**	4.71 **A-549**			
91.	cardiac sapogenins		165.45 **MG-63**						**[25]**
92.		*Periploca forrestii*	3.11 **MG-63**						
93.	steroids	*Strophant hus divaricat us*	1.50 **SGC-7901**	0.93 **K562**	2.74 **HeLa**	1.03 **A-549**			**[26]**
94.			0.04 **SGC-7901**	0.04 **K562**	0.12 **HeLa**	0.06 **A-549**			
95.			1.02 **SGC-7901**	0.58 **K562**	0.86 **HeLa**	1.24 **A-549**			
96.			0.12 **SGC-7901**	0.13 **K562**	0.17 **HeLa**	0.27 **A-549**			
97.			0.08 **SGC-7901**	0.07 **K562**	0.06 **HeLa**	0.19 **A-549**			
98.			1.08 **SGC-7901**	0.79 **K562**	0.82 **HeLa**	1.23 **A-549**			
99.			0.56 **SGC-7901**	0.59 **K562**	0.52 **HeLa**	1.28 **A-549**			
100.			0.39 **SGC-7901**	0.03 **K562**	0.06 **HeLa**	0.14 **A-549**			
101.			20.57 **SGC-7901**	16.08 **K562**	15.13 **HeLa**	22.31 **A-549**			
102.			69.96 **SGC-7901**	38.11 **K562**	69.32 **HeLa**	82.40 **A-549**			
103.			0.21 **SGC-7901**	0.02 **K562**	0.06 **HeLa**	0.33 **A-549**			

Li and colleagues conducted a study where they used (HRESIMS-guided isolation to identify two new bisindole alkaloids of the aspidosperma-scandine type, named epi-scandomelonine **(66)** and epi-scandomeline **(67)**. These compounds were extracted from the leaves and stems of the plant *Melodinus cochinchinensis*. The research showed that these alkaloids, particularly compounds **66** and 6**7**, had a notable toxic effect on the MOLT-4 T-cell leukemia cell line, with IC_{50} values of 5.2 μM and 1.5 μM, respectively, demonstrating higher potency than the standard drug cisplatin, which had an IC_{50} of 4.72 μM **[22]**.

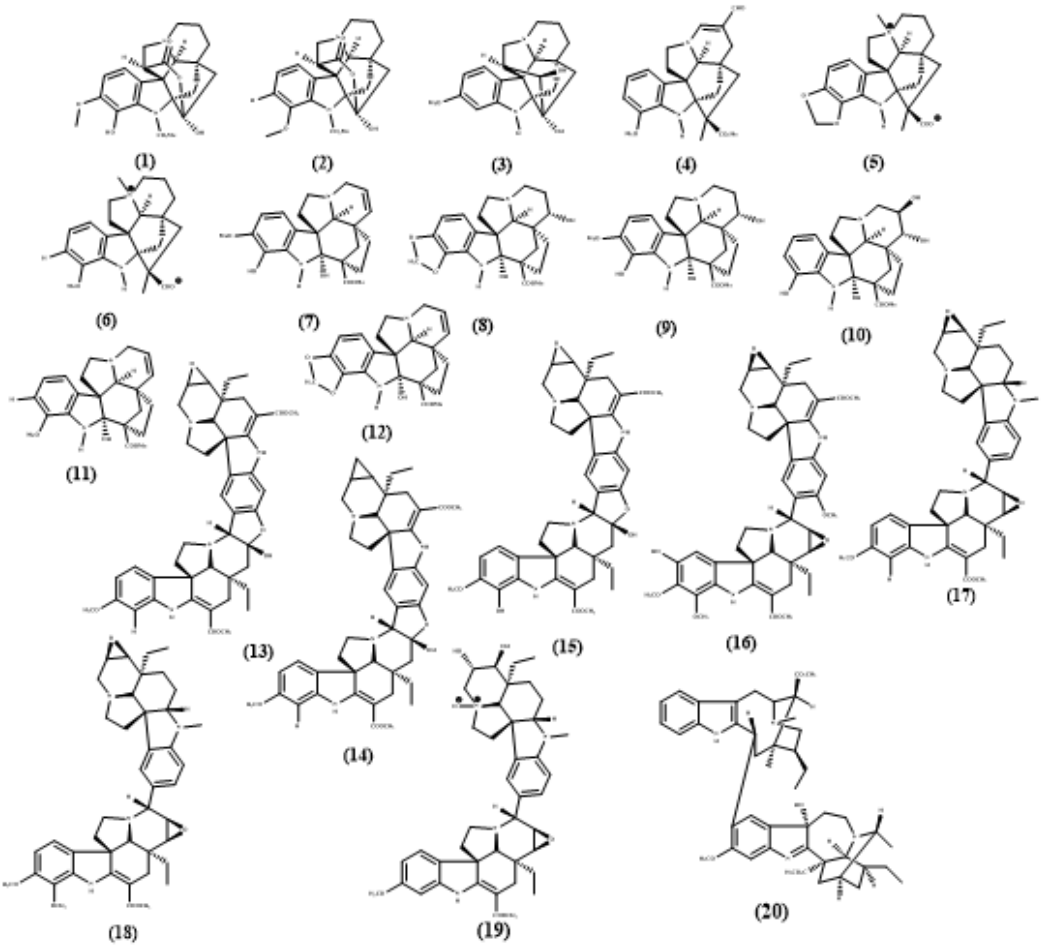
In another study carried out on the aerial parts of *Rhazya stricta*, eight monoterpene indole alkaloids were isolated including two new monoterpene indole alkaloids (6-nor-antirhine-N1-methyl**(69)** and Razyamide **(68)**)**,** in addition to six known indole alkaloids eburenine **(61),** epi-rhazyaminine **(59),** rhazizine **(70),** 20-epi-sitsirikine **(60),** antirhine **(71)**, 16-epi-stemmadenine-N-oxide **(72)** were isolated, The cytotoxic effects were analyzed on MCF-7, HepG2, and HeLa cell lines. Among the isolated compounds, razyamide **(68)** revealed interesting cytotoxic activity against MCF-7, HepG2, and HeLa cell lines with IC_{50} of 5.1, 5.1, and 3.1 μM, respectively. In contrast, the other isolated alkaloids showed moderate to weak activity **[23]**.

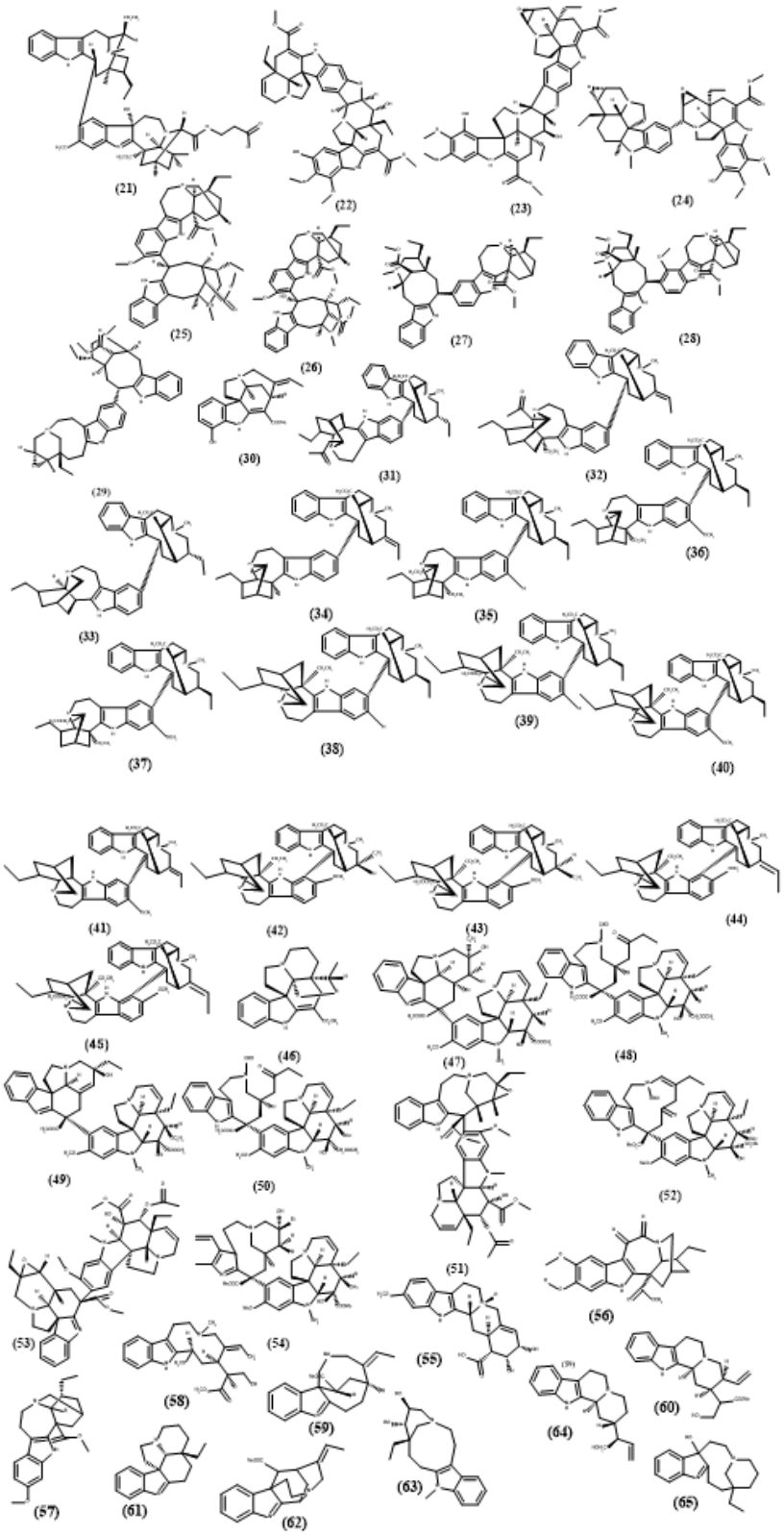
Abdul-Hameed et al. extended their investigation by conducting an in-depth cell cycle analysis to track the effect of razyamide **(68)** on the distribution of cell cycle phases of the cancer cells. The study also provided a differential analysis of cells undergoing apoptosis (programmed cell death) and those succumbing to necrosis (non-programmed cell death). Upon treatment with razyamide **(68),** a notable augmentation in the population of apoptotic cells was observed in MCF-7, HepG2, and HeLa cells (31.4, 29.2, and 34.9%, respectively, when compared to the control group). Furthermore, razyamide **(68)** also induced a significant increase in the necrotic cell population, particularly in cervix cancer cells (HeLa) and hepatocellular carcinoma cells (HepG2). This underscores the potential therapeutic implications of compound **(68)** in cancer treatment **[23]**.

Two new monoterpenoid indole alkaloids

along with eight known analogues were isolated from the leaves and twigs of *Tabernaemontana bovina*. Six of these alkaloids; Taberbovinine B **(73),** 14α,15β-dihydroxy-N-methylaspidospermidine **(74),** (16S)- 15-epi-E-isositsirikine **(75),** (16R)- 15-epi-E-isositsirikine **(76),** hecubine **(77),** and voafinidine **(78)** showed weak cytotoxicity against HepG2, MCF-7, SK-LU-1, SK-Mel-2, and LNCaP, while the rest of alkaloids, Taberbovinine A **(79),** mehranine **(80)**, 16 R-19,20-E-isositsirikine acetate **(81),** voacangarine **(82)** showed no cytotoxicity with IC_{50} > 100 μM **[24]**.

A study conducted on the air-dried herbs of *Melodinus axillaris* led to the discovery and detailed chemical analysis of four novel dimers of monoterpenoid indole alkaloids. (MIAD), Axidimins A, B, C, and D **(83-86)** with a unique apidosperma-aspidosperma type skeleton**.** These compounds exhibited variable cytotoxic activity on HCT116, A549, Hep-G2, and AGS cell lines. Axidimins *C* and D **(85-86)** revealed the most potent cytotoxic activity particularly on the HCT116 cell line (IC_{50} 5.3 and 3.9 μM, respectively), superior to the standards etoposide and 5-fluorouracil **[25] (Fig. 1**).

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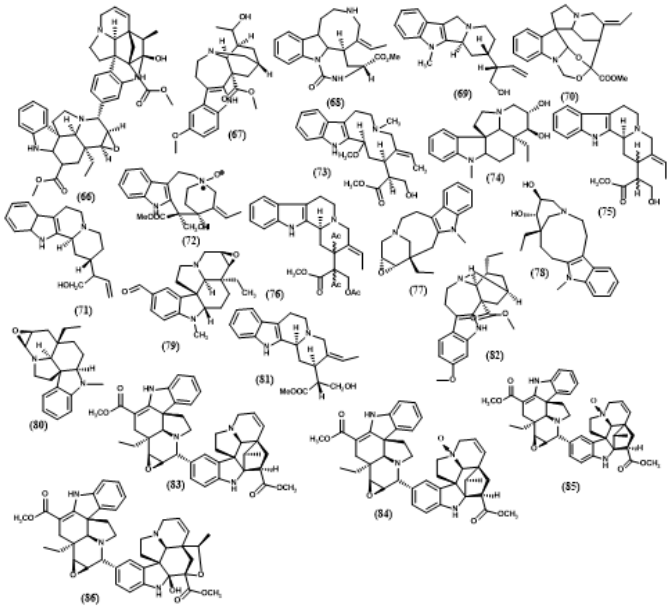

Fig. 1. illustrates the chemical structures of the different cytotoxic indole alkaloids isolated from different members of the family Apocynaceae.

2.2. Cardiac glycosides

In their research, Ran and colleagues identified a total of fifteen substances were identified from *Strophanthus divaricatus* stems. This included four new cardiac glycosides and eleven previously recognized steroids, all of which were tested for their ability to kill various human cancer cell lines, such as K562, SGC-7901, A549, and HeLa. The 4 new cardiac glycosides; 8β-hydroxy-divaricoside **(87),** 8β-hydroxy-17βH-divaricoside **(88),** 17βH-sinoside **(89),** and iso-decoside **(90),** showed promising cancer cell growth inhibition with IC_{50} ranging from 0.2-2.07, 1.49-6.09, 0.57-1.65 and 4.71-23.13 μM, respectively **(Fig. 2**).

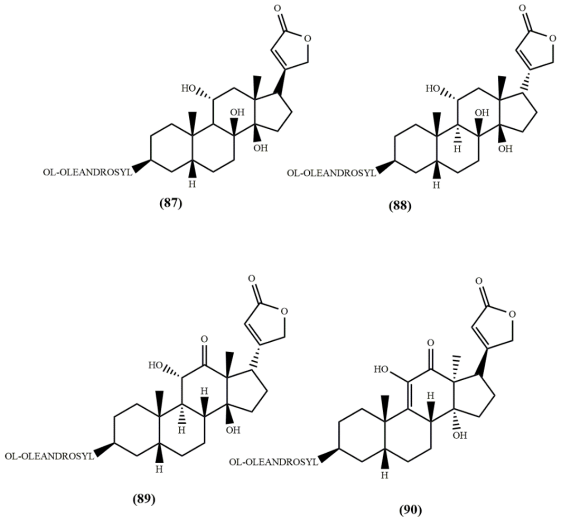

Fig. 2. illustrates the chemical structures of the different cytotoxic Cardiac glycosides isolated from different members of the family Apocynaceae.

2.3. Cardiac sapogenines

The cardiac sapogenins 3β-hydroxy card-5,14,20 (22)-trienolide **(91)** and periplogenin **(92)** are isolated compounds by Jin and colleagues from the stems and roots of Periploca forrestii and assessed their effectiveness in killing osteosarcoma MG-63 cells. While 3β-hydroxycard-5,14,20 (22)-trienolide **(91)** displayed weak cytotoxicity (IC_{50} 165.45 μM), periplogenin **(92)** exhibited a significantly higher cytotoxic effect, (IC_{50} 3.11 μM) superior to that of adriamycin (IC_{50} 36.31 μM). This discrepancy in cytotoxicity suggests that structural modifications at C-5 and C-14 can lead to significant differences in anticancer activity **[26] (Fig. 3.)**.

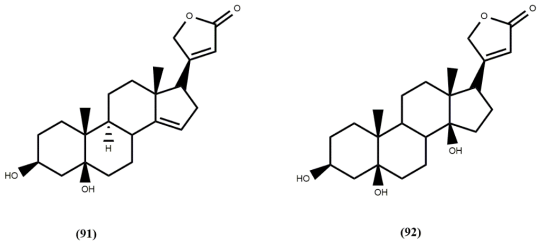

Fig. 3. illustrates the chemical structures of the different cytotoxic cardiac sapogenins isolated from different members of the family Apocynaceae.

2.4. Steroids

In the research by Ran and colleagues, a total of fifteen substances were identified from *Strophanthus divaricatus* stems which include eleven steroids named, sinogenin **(93),** sinoside **(94),** decogenin **(95),** decoside **(96),** ψ-glucoside **(97),** caudoside **(98),** sarmentogenin **(99),** divaricoside **(100),** 17βH-sarmentogenin **(101),** 17βH-divaricoside **(102),** and 5β-card-20 (22)-enolide, 3β-(2,6-dideoxy-3-O-methyl-β-D-xylo-hexopyranosyloxy)- 14-hydroxy-11-oxo-6-ol **(103)** showed cytotoxic activities with different degrees of efficacy and specificity as detailed in **Table 1 [27] and Fig. 4.**. However, the potential cytotoxicity of the reported compounds was not evaluated on normal cells.

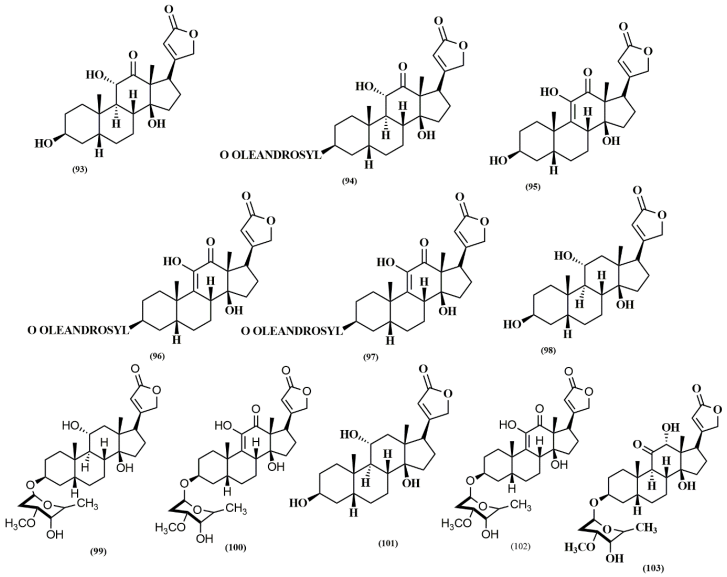

Fig. 4. Illustrates the chemical structures of the different cytotoxic steroids isolated from different members of the family Apocynaceae.

Table 1 summarizes the cytotoxic activities of the different secondary metabolites isolated from family Apocynaceae in the last 5 years.

3. Preclinical Studies

The cytotoxic properties of different compounds isolated from Apocynaceae plants were evaluated using *in vitro* and also *in vivo* models **[28]**. While *in vitro* studies typically use cancer cell lines, *in vivo* studies use animal models to assess the effectiveness and harmfulness of these compounds, Combination therapy, which involves the use of multiple compounds to enhance their cytotoxic effects, has also been studied in preclinical models **[28]**.

A study reported the anticancer activity of plumeride, an iridoid previously isolated from *Plumeria rubra* L., in human breast cancer MCF-7 and human colon cancer HT-29 cells. The study showed that plumeride induced apoptosis and inhibited the ROS/ERK pathways in both cell lines. The study also evaluated the *in vivo* anticancer activity of plumeride in a mouse xenograft model of MCF-7 cells and found that plumeride significantly reduced tumor volume and weight **[29]**.

Zhang and colleagues' research investigated the combined impact of vincristine, sourced from the plant *Catharanthus roseus*, and the compound curcumin on K562 leukemia cells. Their findings revealed that this combination amplified the destructive effects on cancer cells, increased the rate of cell death, and halted cell division. Additionally, when tested in a live mouse model with K562 cell tumors, this dual treatment notably reduced tumor size and extended life expectancy **[30, 31]**.

A study by Wang et al. evaluated the anticancer activity of the cardenolide, 3β,5,14-trihydroxy-19-oxo-card-20(22)-enolide (TTOC), previously isolated from *Nerium oleander*, in human lung cancer (A549) cells. The study revealed that TTOC induced apoptosis, autophagy, and ER stress in A549 cells. The study also examined the *in vivo* antitumor activity of TTOC in a mouse xenograft model of A549 cells and found that TTOC significantly suppressed tumor growth and metastasis **[32, 33]**.

4. Clinical trials

Several compounds derived from Apocynaceae species were evaluated in clinical trials for their potential as anticancer agents. Vinca alkaloids, such as vinblastine and vincristine, two chemotherapy drugs, have been utilized for many years and proven to be successful in treating different forms of cancer **[28]**, Other compounds, belonging to different classes such as diterpenoids and triterpenoids, also showed promise in preclinical studies and are currently being evaluated in clinical trials **[34]**. However, the development of Apocynaceae-based anticancer drugs has been hampered by toxicity and safety concerns, and strategies to minimize these issues are being explored.

5. Toxicity and safety concerns

The cytotoxic compounds produced by different species of the Apocynaceae family can have toxic effects on normal cells and tissues, and strategies to override these effects are urgently warranted **[35]**, Vinca alkaloids, for example, can cause hematopoietic toxicity, neurotoxicity, and gastrointestinal toxicity (Nakajima et al., 2018). Liver and kidney toxicity have also been observed with other compounds, such as diterpenoids and triterpenoids **[34]**, to minimize toxicity, prodrug formulations and nanoparticle delivery systems are being developed.

Conclusion

The Apocynaceae family represents a prolific

source of cytotoxic lead compounds with potential applications in cancer therapy. Recent research has focused on the isolation and characterization of novel bioactive compounds from Apocynaceae plants, as well as evaluating their cytotoxic effects. The cytotoxic efficacy varies depending on the cancer cell line, highlighting the need for further research to test these compounds against the same target cell lines and under the lens of the same *in vitro* assays which will optimize their potential applications in cancer therapy. The development of novel drug delivery systems and the investigation of synergistic effects with other chemotherapeutic agents or targeted therapies are also important areas of future research.

Joint efforts and the integration of different scientific fields are key to finding and creating new compounds from natural sources that can combat cancer. Chemists, biologists, pharmacologists, and clinicians must work together to identify and optimize potential lead compounds, evaluate their efficacy and safety in preclinical and clinical studies, and translate them into effective cancer therapies. Additionally, collaboration with indigenous communities and conservationists is crucial to ensure the sustainable use of natural products and protect biodiversity.

The primary objective of this review is to offer an exhaustive analysis of the cytotoxic attributes inherent to the Apocynaceae plant family, thereby assessing their prospective utility as a reservoir of anticancer therapeutics. The review accentuates the imperative nature of persistent research in this domain, given the potential these botanical species hold in the genesis of efficacious anticancer treatments.

Moreover, it underscores the necessity for meticulous evaluation of the potential cytotoxicity these compounds may exert on healthy cellular structures, as well as their potential interactions with existing chemotherapeutic agents. This review, therefore, serves as an invaluable asset for scholars and practitioners in the realm of oncological therapy and drug development.

It not only encapsulates the current state of knowledge but also pinpoints the lacunae in our present understanding, thereby delineating the trajectory for future investigative endeavors. This comprehensive review, thus, stands as a testament to the potential of Apocynaceae plants in revolutionizing the landscape of cancer therapeutics. It not only summarizes the current state of knowledge but also identifies gaps in the current understanding and outlines directions for future research. This review serves as a valuable resource for researchers in the field of cancer therapy and drug development. It not only summarizes the current state of knowledge but also identifies gaps in the current understanding and outlines directions for future research.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data are included in this published article in the main manuscript.

Conflict of Interest

The authors assert that there are no conflicts of interest.

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Authors Contribution

Neamtullah Wael: Writing - original draft, manuscript revision. Ahmed Elissawy: review idea and outline & editing, Supervision. Nehal Ibrahim: review & editing, Supervision. Abdel Nasser Singab: review & editing, Supervision. All authors approved the final manuscript.

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