JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Review Article

A review on ethnobotany, pharmacology and phytochemistry of *Tabernaemontana corymbosa*

Ibrahim Babangida Abubakar[a,*] and Hwei-San Loh[a,b,*]

[a]School of Biosciences, Faculty of Science, The University of Nottingham Malaysia Campus and [b]Biotechnology Research Centre, The University of Nottingham Malaysia Campus, Semenyih, Selangor, Malaysia

Keywords
alkaloids; anticancer; ethnomedicine; phytochemistry; *T. corymbosa*

Correspondence
Hwei-San Loh, School of Biosciences, The University of Nottingham Malaysia Campus, Jalan Broga 43500 Semenyih, Selangor, Malaysia.
E-mail: Sandy.Loh@nottingham.edu.my

Received November 9, 2015
Accepted January 14, 2016

doi: 10.1111/jphp.12523

*Both authors have equal contribution.

Abstract

Objectives *Tabernaemontana* is a genus from the plant family, *Apocynaceae* with vast medicinal application and widespread distribution in the tropics and subtropics of Africa, Americas and Asia. The objective of this study is to critically evaluate the ethnobotany, medicinal uses, pharmacology and phytochemistry of the species, *Tabernaemontana corymbosa* (Roxb. ex Wall.) and provide information on the potential future application of alkaloids isolated from different parts of the plant.

Key findings *T. corymbosa* (Roxb. ex Wall.) parts are used as poultice, boiled juice, decoctions and infusions for treatment against ulceration, fracture, postnatal recovery, syphilis, fever, tumours and orchitis in Malaysia, China, Thailand and Bangladesh. Studies recorded alkaloids as the predominant phytochemicals in addition to phenols, saponins and sterols with vast bioactivities such as antimicrobial, analgesic, anthelmintic, vasorelaxation, antiviral and cytotoxicity.

Summary An evaluation of scientific data and traditional medicine revealed the medicinal uses of different parts of *T. corymbosa* (Roxb. ex Wall.) across Asia. Future studies exploring the structure-bioactivity relationship of alkaloids such as jerantinine and vincamajicine among others could potentially improve the future application towards reversing anticancer drug resistance.

Introduction

The medicinal application of plants for treatment of various ailments dates back to thousands of years. Ancient medication involved the use of crude extract as decoctions, powders, tea, tinctures among other numerous herbal formulations[1] and documented evidences dating back to 1100 BC have illustrated over 600 medicinal plants in Chinese medicine.[2] A large proportion of people from developing countries in Africa and Asia still depend on plants as a source of medication. Phytochemical studies from the synthetic era have resulted in isolation of natural therapeutic agents and over 60% of approved chemotherapeutic agents are derived from natural sources.[3] The Asian flora is among the foremost destination in the world that is highly endowed with a vast number of plants with high medicinal uses including Moraceae and Apocynaceae. The Apocynaceae, represents a plant family with over 150 species in 150 genera and one-third of these occurs in Africa with about 40 species in 22 genera in Kenya.[4] The genus, *Tabernaemontana* comprises of 100 species with a widespread distribution in the tropical and subtropical parts of Asia, Africa, Americas, Oceania and Australia. In fact, about 13 different species are found in Malaysia.[5] Documented phytochemical studies have shown *Tabernaemontana* as a source of novel structured indole and bisindole alkaloids possessing interesting bioactivities with the most notably anticancer property.[6] The species, *T. corymbosa* has attracted research interest among phytochemists in producing novel compounds. However, to date, there is no comprehensive study highlighting the ethnobotanical and ethnomedicinal values of this plant. The present review aimed to discuss about the general traditional use, pharmacology and phytochemistry of *T. corymbosa* as well as the underlying mechanisms of action for the Aspidosperma type alkaloids towards reversal of drug resistance in vincristine-resistant cancers.

Methodology

Firstly, the synonyms of *T. corymbosa* were confirmed through plant data base (www.theplantlist.org). Thereafter, published articles on *T. corymbosa* were retrieved using popular search engines as well as relevant science search engines and database including google scholar, ISI web of knowledge, Science direct and PubMed. A total of 117 articles were retrieved over a period of 2 years (2013–2015), but only 62 were considered for this review upon a criterion where published articles on *T. corymbosa* or its synonyms with at least three point confidence level as listed in theplant list.org. In addition, data on the same isolated compounds but published using different plant synonyms were streamlined to avoid duplication. Data were collated into ethnobotany; pharmacology and phytochemistry groups and tabulated using Microsoft excel 2010 software.

Ethnobotany and medicinal uses of *Tabernaemontana corymbosa*

Morphologically, *T. corymbosa* (Roxb. ex Wall.) is a wild plant growing as shrub or small tree with a height of 3 m. The plant is glabrous except for its soft scented flowers; it generally grows throughout the year. *T. corymbosa* (synonyms: *Ervatamia corymbosa* King and Gamble, *Ervatamia longopedicellata Ly, Ervatamia phuongii Ly, Ervatamia chinensis, Tabernaemontana laotica* Pitard, *Tabernaemontana baviensis* Pitard, *Pagiantha corymbosa* (Roxb. ex Wall) Markgr)[7–9] grows in a habitat of mix wood and brushwoods (500–700 m) and is predominantly found in Indonesia, Laos, Thailand, Vietnam, Malaysia and China.[10] The plant is known by the local names as 'jelutong badak', 'pokok gading', 'resting', 'susun kelapa', 'pelir kambing' in Malaysia.[11,12] In addition, other local names include 'san fang gou ya hua' (Chinese),[7] 'Kath-mollicka', and 'Dudh phool' (Bangladesh),[13,14] 'sang laa' (Thailand peninsular) and 'l[af]i tr[aa]u t[as]n' (Vietnam).[11] In Malaysia, the plant can be found in Terengganu, Tekam Forest in Pahang, Chenderiang in Perak, Gunung Stong in Kelantan, Johor and Jeram Kedah in Negeri Sembilan. Similarly, in China, the plant is found in western Guangxi, southwest Guizhou, and Yunnan provinces, as well as in the northern part of Thailand.[15]

Globally, almost all parts of *Tabernaemontana* species such as fruits, leaves, sap, latex, stem bark, root bark and whole plants are used for ethnomedicinal purposes. *Tabernaemontana* species have a vast range of traditional medicinal applications that include using as decoctions and steam water baths for wound healing and treatment of syphilis, respectively. Ethnobotanical data on the uses of 75 *Tabernaemontana* species [16] showed that up to 78% was for medicinal purpose, whereas, 22% was for non-medicinal purpose. The species were mostly used to treat diseases, classified as antimicrobial, antiparasitic and analgesic in Africa. Whereas, antimicrobial, central nervous system (CNS), febrifuge, antitumour, and analgesic were mostly treated in Americas and the Asia/Australia and Pacific regions (Figure 1). Medicinal application of the genus, *Tabernaemontana* in Thai, Ayurvedic and Chinese traditional medicines includes treatment of ailments such as fever, pain, dysentery and etc.[16] While, in Africa, decoction from roots, latex from fruits or grounded leaves from indigenous species are used as remedy for headache, constipation, flatulence and stomach ache. In fact, a mixture of leaf powder with other species is soaked in water and used to treat bewitched persons or consumed daily to revive appetite.[4] In peninsular Malaysia, decoction of bark from *T. malaccensis* and *T. corymbosa* is used to treat syphilis, whilst the steam from boiled juice is inhaled to treat ulceration of the nose.[16] Parts of *T. corymbosa* are processed into different forms that include pounded roots, infusions of bark or roots, poultice of leaves and decoction of the bark for treatments of syphilis ailments, ulceration and postnatal recovery.[17] The roots are processed as decoction and administered orally for treatment of fever [12] while a paste of the plant is used to treat orchitis.[7] In Bangladesh, the leaves are used for treatment of tumours.[14] Whereas, the juice extracted from crushed roots is taken orally for treatment of jaundice by locals residing in Mirzapur Village of Dinajpur District.[13] The sap from the leaves is used for treatment of sores.[11] In Guangxi China, the leaves and bark of *T. corymbosa* are used to treat fractures.[7] On the other hand, the use of root extracts or latex as arrow poison and birdlime, respectively, only exemplifies its non-medicinal applications in Malaysia and Thailand. These medicinal and non-medicinal uses have been summarized as in Table 1.

Pharmacological activity

Medicinal plants are continuously been explored as sources for new chemotherapeutic agents. Over the years, there have been pharmacological and phytochemical reports on the vast medicinal potential of *Tabernaemontana* species to different types of ailments. Indeed, studies conducted on extracts or pure compounds of *T. corymbosa* have reported pharmacological activities that included cytotoxicity, anthelmintic, analgesic and antinematodal activities among others (Table 1).

Antioxidant activity

Diseases such as inflammation, cancer, diabetes have been related to oxidative damage caused by free radicals. Recent study demonstrated the high antioxidant potency of

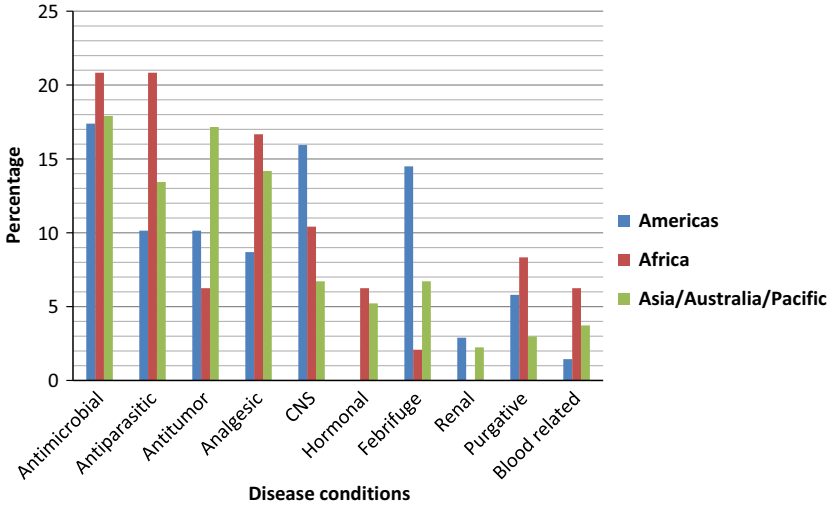

Figure 1 Disease conditions treated by *Tabernomantana* species in traditional medicine at different regions.

Table 1 Summarized bioactivities, medicinal and non-medicinal uses of different parts of *Tabernaemontana corymbosa*

Bioactivities			Medicinal uses			Non-medicinal uses	
Parts of plant	Phytochemical constituents	Pharmacological activities	Parts of plant	Preparation methods	Disease conditions	Parts of plant	Uses
Leaf, stem bark, twigs and whole plant	Alkaloids	• Anticancer • Vasorelaxation	Leaf	Sap and poultice	• Tumour • Sore • Fractures • Postnatal recovery	Root	• Arrow Poison
Stem bark	Alkaloid crude extract	• Antimicrobial • Antifungal • Anticancer	Bark	Decoction, boiled juice and infusions	• Syphilis • Ulceration, fractures		
Leaf, seed, stem, flower and root	Methanol extract	• Antiviral • Antinematodal Antihelmintic • Analgesic	Root	Pounded, decoction and crushed root juice	• Syphilis • Fever • Jaundice • Postnatal recovery	Latex	Birdlime
			Unspecified	Boiled juice and paste	• Fever • Orchitis		

methanol extracts from roots and leaves of *T. corymbosa* due to its total phenolic content. A significant positive correlation was observed between the total phenolic content, 2,2-diphenylpicrylhydrazyl (DPPH) free radical scavenging and ferric reducing potency.[18]

Antimicrobial activity

In a recent *in vitro* study, the disc diffusion method was adopted to evaluate the antimicrobial potency of crude alkaloid extract from stem bark of *T. corymbosa* against four strains (*Bacillus cereus, Pseudomonas aeruginosa, Staphylococcus aureus* and *Escherichia coli)* of bacteria and two types (*Cryptococcus neoformans* and *Candida albicans)* of fungi. The crude alkaloidal extracts demonstrated antimicrobial activity and exhibited zone inhibition in a range of 7.00–14.75 mm as well as minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC)/minimum fungicidal concentration (MFC) ranges of 0.37–1.11 mg/ml and 3.33–10.00 mg/ml, respectively.[19]

Antiviral activity

Viruses continually cause diseases despite development of antiviral vaccine through process such as biopharming and massive vaccination campaigns. Plants have been shown to possess antiviral properties that could potentially serve as sources of drugs against viruses. An *in vitro* study used different treatments mimicking different stages of measles virus to evaluate the antiviral potency of methanol extracts

of leaves from *T. corymbosa*. Scores of 2+ (moderate effect) and 4+ (high effect) were observed for the extracts in treatments mimicking post viral infection and ability of virus to attach to and infect host cells, respectively, demonstrating the antiviral potency of the extracts.[17]

Antinematodal activity

The nematode, *Bursaphelenchus xylophilus* causes serious wilting diseases to the Japanese pine. Although commercially available chemicals were used to mitigate such effects, the negative effect on the ecological system and killing of vectors such as longhorn beetle have made it undesirable. In an effort to search for effective controlling methods, the antinematodal effects of 65 different plant extracts including *T. corymbosa* against *Bursaphelenchus xylophilus* were investigated. Results from the study demonstrated strong antinematodal effects of the methanol extracts from the seeds of *T. corymbosa* with a medium effective dose of 5 mg/cotton ball (mg/bl), whereas, no activity was recorded for sap extracts.[20]

Anthelmintic and analgesic activities

In a previous study, an evaluation of anthelmintic activity revealed a significant dose dependent effect of fresh methanol extracts from leaves of *T. corymbosa* compared to control drug, albendazole. Furthermore, methanol extracts of leaf, stem and flower of *T. corymbosa* exhibited significant *in vivo* analgesic effects compared to control drug, diclofenac-Na upon investigation using tail-flick and hot-plate tests.[21]

Vasorelaxation

Recent studies on bioactivities of isolated alkaloids have demonstrated their potency to induce vasorelaxation. For instance, vernavosine ethyl ester isolated from stem bark of the Malayan *T. corymbosa* induced moderate dose dependent relaxation effects on phenylephrine-induced contraction in rat aortic rings with an EC_{50} value of 2.48 μM.[22] Similarly, rutaecarpine recently isolated from whole plant of the Chinese *T. corymbosa* [23] has been previously shown to induce vasorelaxation in phasic and tonic phases of phenylephrine-induced contraction (1 μM–0.1 mM) via an endothelium dependent mechanism that involves nitric oxide and gaunylyl cyclase.[24]

Cytotoxicity

Plants have been explored as potential sources for cytotoxic agents and in fact contributed to 40% of the available anticancer drugs from 1940 to 2002.[1] Several studies have investigated the cytotoxic potency of different crude extracts and purified alkaloids from different parts of *T. corymbosa*. Crude alkaloid extracts from stem bark extracts induced cytotoxic effects on human lung adenocarcinoma (A549) and human cervical carcinoma (C33A) cancer cells with IC_{50} values of 7.81 and 3.91 μg/ml, respectively.[19] Similarly, as shown in Table 2, purified alkaloids isolated from different parts of *T. corymbosa* induced potent cytotoxic effects against different types of cancer cells including vincristine-sensitive KB/S and vincristine-resistant KB/VJ300 human carcinoma oral epidermoid cells.[25–28] On the other hand, there are contrasting studies on the potential toxicity of *T. corymbosa* to normal cells. For instance, methanol extracts from leaves did not induce toxicity to brine shrimp ($CTC_{50} > 1000$ mg/ml) or Vero cell lines derived from monkey kidney ($IC_{50} > 100$ μg/ml).[17,29] This is contrary with another study where the toxicity of methanol extracts of leaf, stem and flower to brine shrimp was reported with IC_{50} values ranging from 0.35–0.57 μg/ml.[21] In addition, a recent study also demonstrated the toxicity of jerantinine derivatives to non-cancerous human lung fibroblast (MRC-5) cells.[30] Regardless of the potential toxicity of the purified alkaloids to normal cells, the anticancer potency of these alkaloids can still be explored whilst minimizing toxicity via synergism and more efficient targeted delivery mechanisms.

Phytochemistry

Alkaloids of *T. corymbosa*

The phytochemical constituents of *Tabernaemontana* are predominantly alkaloids and studies from the 19th century have produced over 200 alkaloids with varying complex structures. The history of medicinal uses of *T. corymbosa* prompted the isolation and elucidation of mechanisms of action of potential natural compounds responsible for its medicinal properties. In fact, over the past 20 years, majority of published literatures on alkaloids originated from *Tabernaemontana* have largely contributed from the Malayan *T. corymbosa* in addition to alkaloids isolated from other species.[31] Although alkaloids are the predominant and most studied phytochemicals of *T. corymbosa*, studies have also reported the presence of saponins, phenolics and sterols.[17,18,32] Available literature on phytochemical constituents of *T. corymbosa* also showed the impact of location and time in determining the type of alkaloids produced. For instance, a recent study reported that *T. corymbosa* collected at different time and from different locations (Tekam Forest, Pahang and Chenderiang, Perak) in Malaysia produced vast number of different novel alkaloids in addition to similar iboga, corynantheine, vobasine, strychnos alkaloids.[5]

Table 2 Cytotoxic alkaloids isolated from whole plant, leaf, stem bark and twig parts of *Tabernaemontana corymbosa*

No.	Parts of plant	Location of collection	Types	Alkaloids	IC_{50} (μM) on cell types							Ref.
					KB/S	KB/VJ300	KB/VJ300[ab]	Lung	Liver	Breast	Colon	
1	Leaf	Tekam Forest, Pahang Malaysia	Aspidosperma indole	Jerantinine A	1.99	1.73	–	–	–	–	0.43 (VR-HCT-116)	[25] [49]
				Jerantinine B	1.11	0.95	–	–	–	–	0.49 (VR-HCT-116)	[25]
				Jerantinine C	0.81	1.54	–	–	–	–	–	
				Jerantinine D	0.68	0.95	–	–	–	–	–	
				Jerantinine E	2.55	2.03	–	–	–	–	–	
				Jerantinine F	12.80	12.30						
				Jerantinine A-acetate	1.04	0.83	–	–	–	–	–	
				Jerantinine B-acetate	0.70	0.75	–	–	–	–	–	
				10-*O*-methyl jerantinine A	12.0	13.6	–	–	–	–	–	
				10-*O*-methyl jerantinine B	7.36	10.70	–	–	–	–	–	
2	Stem bark	Tekam Forest, Pahang, Malaysia	Hexacyclic indole	Conolutinine	NA	NA	51.25[a]	–	–	–	–	[26]
3	Stem bark	Malaysia	Indole	Lirofolines A	NA	NA	10.45[a]	–	–	–	–	[28]
				Lirofolines B	NA	NA	21.11[a]	–	–	–	–	
4	Whole plant	Yunnan province, China	Indole	Ervachinine E	–	–	–	11.22 (A549)	13.61 (SMMC-7721)	14.44 (MCF-7)	14.70 (SW480)	[23]
5	Bark	Johor, Malaysia	Pentacyclic indole	Voatinggine	>80.00	–	–	–	–	–	–	[57]
				Tabertinggine	>58.00	–	30.94[a]	–	–	–	–	
6	Leaf	Yunnan province, China	Indole	Tabercarpamine A	–	–	–	–	3.31 (HepG2) 6.76 (SMMC-7721)	8.54 (MCF-7)	–	[58]
7	Leaf	Yunnan province, China	Monoterpene indole	Bistabercarpamine A	–	–	–	–	38.14 (HepG2)	–	–	[59]
8	Stem bark	Johor, Malaysia	Indole	Criofolinine	>60.00	>60.00	–	>60.00 (A549)	–	–	>60.00 (HCT-116)	[22]
				Vernavosine	>60.00	–	–	>60.00 (A549)			>60.00 (HCT-116)	
9	Stem bark	Tekam Forest, Pahang, Malaysia	Indole	Vincamajicine	>70.00	>70.00	2.62[a]	–	–	–	–	[5]
				Cononusine	>70.00	>70.00	>70.00[a]	–	–	–	–	
				Ervaluteine	>70.00	>70.00	53.20[a]	–	–	–	–	
				Tacamonidine	>70.00	>70.00	>70.00[a]	–	–	–	–	
10	Leaf	Malaysia	Vobasine-iboga bisindoles	Conodiparine A	25.59	17.99	1.93[b]	–	–	–	–	[27]
				Conodiparine B	27.69	19.98	3.26[b]	–	–	–	–	
				Conodiparine C	28.58	22.69	7.48[b]	–	–	–	–	
				Conodiparine D	24.84	18.16	6.14[b]	–	–	–	–	
11	Whole plant	Yunnan province, China	Vobasinyl–ibogan bisindole	Ervachinine A	–	–	–	2.86 (A549)	3.35 (SMMC-7721)	3.20 (MCF-7)	2.39 (SW480)	[60]
				Ervachinine B	–	–	–	15.98 (A549)	11.40 (SMMC-7721)	15.17 (MCF-7)	15.33 (SW480)	
				Ervachinine C	–	–	–	0.84 (A549)	3.46 (SMMC-7721)	3.25 (MCF-7)	3.66 (SW480)	
				Ervachinine –D	–	–	–	3.10 (A549)	4.63 (SMMC-7721)	11.76 (MCF-7)	3.63 (SW480)	

Table 2 (*Continued*)

No.	Parts of plant	Location of collection	Types	Alkaloids	IC_{50} (μM) on cell types							Ref.
					KB/S	KBVJ300	KBVJ300[ab]	Lung	Liver	Breast	Colon	
12	Stem bark	Taiping, Perak, Malaysia	Indole	Vobasidine A	15.48	>70.00	>70.00[a]	–	–	–	–	[61]
			Bisindole	Vobasidine B	53.67	>70.00	>70.00[a]	–	–	–	–	
				Vobasidine C	15.53	>70.00	26.54[a]	–	–	–	–	
				16-epivobasine	15.90	62.47	38.33[a]	–	–	–	–	
				Taipinisine	44.22	>70.00	18.57[a]	–	–	–	–	
				Tabernaemontanine	>70.00	>70.00	>70.00[a]	–	–	–	–	
				Dreagamine	>70.00	>70.00	>70.00[a]	–	–	–	–	
				Vobasine	>70.00	>70.00	>70.00[a]	–	–	–	–	
				Vobasenal	>70.00	>70.00	>70.00[a]	–	–	–	–	
				16-epivobasenal	14.48	>70.00	>70.00[a]	–	–	–	–	
13	Stem bark	Tekam Forest, Pahang, Malaysia	Vobasinyl-iboga isindole	Ervatensine A	1.39	1.21	0.98[a]	–	–	–	–	[5]
				Ervatensine B	0.95	1.11	1.20[a]	–	–	–	–	
14	Leaf and twig	Xishuangbanna, Yunnan, China	Vobasinyl-ibogan binsindole	Tabercorine A	–	–	–	4.14 (A549)	3.53 (SMMC-7721)	8.10 (MCF-7)	9.24 (SW480)	[62]
				Tabercorine B	–	–	–	10.34 (A549)	13.31 (SMMC-7721)	4.70 (MCF-7)	16.93 (SW480)	
				Tabercorine C	–	–	–	33.16 (A549)	31.52 (SMMC-7721)	>40.00 (MCF-7)	>40.00 (SW480)	

Cell lines: KB/S, vincristine-sensitive human oral epidermoid; KBVJ300, vincristine-resistant human oral epidermoid; SMMC-7721, human hepatocellular carcinoma; HepG2, human hepatocellular liver carcinoma; HL-60, human myeloid leukaemia; A549, human lung adenocarcinoma; MCF-7, human breast adenocarcinoma; SW480, human colon adenocarcinoma; HCT-116, human colorectal carcinoma; VR-HCT-116, vincristine-resistant human colorectal carcinoma. NA, no activity; (–), not reported. KBVJ300: [a]with addition of vincristine (0.12 μM) as adjunct treatment; [b]with addition of vincristine (0.30 μM) as adjunct treatment.

The potential of reversing anticancer drug resistance

Phytochemical studies on leaves and stem bark of *T. corymbosa* employing complex isolation techniques have produced a pool of novel structured alkaloids with interesting anticancer activities that include the reversal of drug resistance in vincristine-resistant KB/VJ300 cells as shown in Table 2. Majority of these isolated alkloids are indoles of different types such as aspidosperma, pentacyclic, hexacyclic, iboga-pyrrolidone conjugate, iboga, bis-vobasinyl-chippiine, hexacylic chippiine derivative, chippiine, vobasine and tacaman.[6,15,33–45] The bisindoles constituted the second largest group of alkaloids comprising mainly of vobasinyl-ibogan types.

Following decades of research, anticancer drug resistance has generally been categorized into two major groups of intrinsic and acquired drug resistance. Intrinsic drug resistance is associated with cell cycle and cell adhesion among other mechanisms. Whereas, alteration of drug targets, reduced drug accumulation, increased detoxification and subsequent reduction in apoptosis represent acquired drug resistance.[46] Whilst efforts at clinical levels include minimizing administration dosage to avoid drug resistance, the efflux effects of the p-glycoprotein/MDR (multidrug resistance) continue to block the potential of anticancer drugs. Although action of enzymes like topoisomerase I and II, gluthatione and increased DNA damage repair contribute to drug resistance, expression and efflux action of p-glycoprotein are arguably the most researched cellular drug resistance.[47] Vincristine, vinblastine, taxanes and paclitaxel are among the group of microtubule stabilizing and destabilizing chemotherapeutic drugs that exhibit MDR cross-resistance phenotype due to p-glycoprotein.

Increased expression of MDR gene in KB cells causes resistance to vincristine, whereas, indole and bisindole alkaloids such as jerantinine A-F (leaf extract), conodiparines A-D (leaf extract), lirofolines A (stem bark) and vincamajicine (stem bark) isolated from *T. corymbosa* caused reversal of vincristine resistance in human KB/VJ300 cells. Thus far, the Aspidosperma type indole alkaloids jerantinine (A-F) (structures are shown in Figure 2) and the acetate derivatives of jerantinine A and B demonstrated the most potent effect with $IC_{50} < 1$ μg/ml.[25] Although these alkaloids demonstrated strong potency in reversing drug resistance, to date, very few studies have explored the mechanism of action of jerantinine. Preliminary study on synthetic jerantinine E suggested the disruption of microtubules and inhibition of polymerization as a possible mechanism of action.[48] Further mechanistic study on the effect of jerantinine A on human colorectal carcinoma (HCT-116) and breast adenocarcinoma (MCF-7) cancer cells confirmed microtubule disruption, inhibition of tubu-

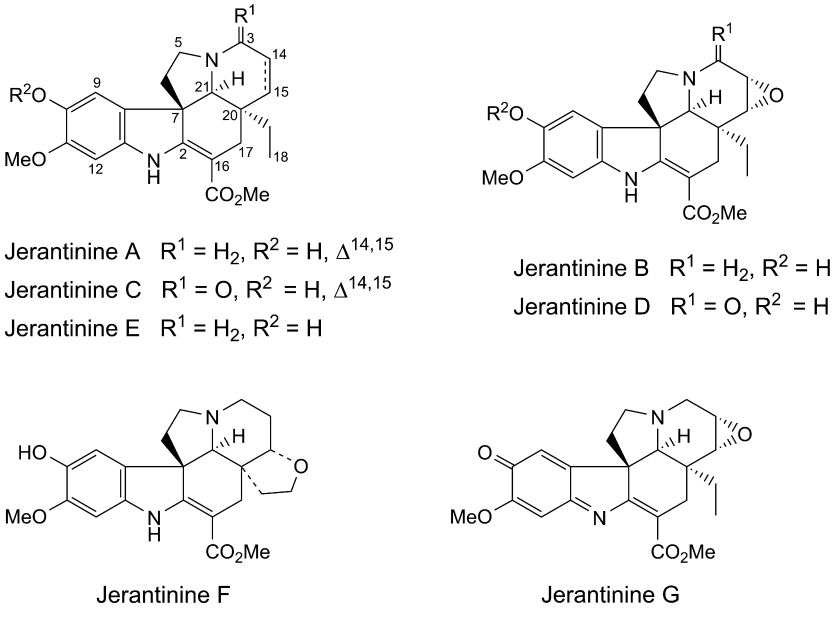

Figure 2 Structures of jerantinine (A-G).[25]

lin polymerization, profound G2/M arrest, aneuploidy and down regulation of cyclin B1.[30] Similarly, a recent study confirmed that jerantinine B (an analogue of jerantinine A) serving as a microtubule targeting agent (MTA), evokes G2/M arrest, polo-like kinase 1 inhibition and increased reactive oxygen species in HCT-116, MCF-7 and MIA PaCa-2 (human pancreatic carcinoma) cells.[49] Investigation on the growth inhibitory effects of jerantinine and vincristine against variant vincristine-resistant HCT-116 (VR-HCT-116) showed that both jerantinine A (0.43 μM) and jerantinine B (0.49 μM) induced higher level of potent growth inhibition than that of vincristine (1.64 μM)[49]. VR-HCT-116 like KB/VJ300 expresses p-glycoprotein[50] possessing over 300-fold resistance to vincristine and thus considering the similarities in structure and mechanism of action as MTAs for both vincristine and jerantinine, this suggests an alternative mechanism of action that evades the efflux action of the p-glycoprotein. Interestingly, simple acetylation of jerantinine A and B enhanced the cytotoxic potency[25,30,49] in contrast with *O*-methylation that resulted in reduction of cytotoxic activity.[25] In fact, acetylation provides stability and membrane penetration capacity suggesting that acetate derivatives of jerantinine A and B are suitable to act as prodrugs that would require esterase activation.[49,51] On the other hand, there are no studies on possible mechanism for reversal of drug resistance by conodiparines and lirofolines A. This is not surprising because unlike jerantinine, other alkaloids of *T. corymbosa* as shown in Table 2, were not found to have significant effects against vincristine-resistant cells. Although the addition of at least 0.12 μM of vincristine in adjunct treatment studies had shown an improved activity, this effect was unlikely insignificant towards cell growth inhibition as compared to that of the single treatments.[5,61] This indicates that such improved activity may be resultant of an additive effect rather than a synergism of the combined treatments with vincristine. Nonetheless, this is worthy of further research taking into consideration that the current batch of anti-microtubule drugs under development such as vinflunine are synthetic derivatives of established microtubule inhibiting drugs.[52]

The novel skeletal structures of the aforementioned alkaloids are vital to confer the respective anticancer potencies. For instance, previous studies have illustrated that intact aromatic and 16-methyl ester function are essential to the reversal of drug resistance by ibogan structured alkaloids such as coronaridine and 19-*epi*-heyneanine.[53] However, to date, there is no published literature on the potential role of structures of conodiparines, lirofolines A, vincamajicine and especially jerantinine in reversing vincristine drug resistance. Understanding the mechanism of action of these novel alkaloids would enhance the potency and aid in development of potentially new drugs that reverse drug resistance. However, it is noteworthy to mention that in addition to p-glycoprotein, the potential roles of other proteins in conferring anticancer drug resistance have been identified. For instance, high level of the cell surface protein, survivin confers resistance to anticancer drugs and studies have illustrated that blocking or inhibition of survivin enhances response to chemotherapeutic agents.[54] In addition, high dosage delivery and pattern of delivery significantly affect the level

of therapeutic dose in circulation and efforts to circumvent these limitations including synergistic combination with direct or indirect acting drugs at lower dosage and application of nanoparticle delivery systems such as graphene [55,56] can be adopted. Regardless of the aforementioned limitations, this nonetheless illustrates the potential role of these novel alkaloids towards anticancer therapy which further signifies the medicinal importance of *T. corymbosa*.

Conclusion

Tabernaemontana corymbosa has been a source of novel indole and bisindole alkaloids with interesting bioactivities most notably anticancer thus making it an absolute priority to elucidate the mechanisms of action for drug development purpose. Future biological studies aimed at understanding the mechanism of action and potential role of the structure of the alkaloids towards the reversal of anticancer drug resistance in vincristine-resistant KB/VJ300 cells, in addition to other bioactivities would provide valuable information in developing more improved chemotherapeutic agents.

Declarations

Acknowledgements

We are thankful to Dr Kuan-Hon Lim (School of Pharmacy, The University of Nottingham Malaysia Campus) for valuable suggestions to improve this review paper.

Funding

This research received no specific grant from any funding agency in the public, commercial, or non-profit sectors.

References

1. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. *Life Sci* 2005; 78: 431–441.
2. Cragg G *et al.* Natural products in drug discovery and development. *J Nat Prod* 1997; 3864: 52–60.
3. Rocha AB *et al.* Natural products in anticancer therapy. *Curr Opin Pharmacol* 2001; 1: 364–369.
4. Omino EA, Kokwaro JO. Ethnobotany of Apocynaceae species in Kenya. *J Ethnopharmacol* 1993; 40: 167–180.
5. Lim K-H *et al.* Ibogan, tacaman, and cytotoxic bisindole alkaloids from Tabernaemontana. Cononusine, an iboga alkaloid with unusual incorporation of a pyrrolidone moiety. *J Nat Prod* 2015; 78: 1128–1138.
6. Kam T-S, Sim K-M. Conodurine, conoduramine, and ervahanine derivatives from Tabernaemontana corymbosa. *Phytochemistry* 2003; 63: 625–629.
7. Wiart C. *Ethnopharmacology of Medicinal Plants Asia and the Pacific*. Hackworth J, ed. Totowa, New Jersey: Humana Press Inc., 2006.
8. World Conservation Monitoring centre. Tabernaemontana corymbosa. The IUCN Red List of Threatened Species. Version 2015.2. 1998. Available at: www.iucnredlist.org.
9. The Plant list version 1.1. 2013. Available at: http://www.theplantlist.org/. Accessed January 3, 2015.
10. Shu gou ya hua. TABERNAEMONTANA Linnaeus, Sp. Pl. 1: 210. 1753. *flora of china* 1995; 16: 152–153.
11. Chua LSL, Horsten SFA. *Tabernaemontana corymbosa Roxb. ex Wallich [Internet] Record from Proseabase*. van Valkenburg JLCH., Bunyapraphatsara N, eds. Bogor, Indonesia: PROSEA (Plant Resources of South-East Asia) Foundation, 2001. Available at: http://www.proseanet.org.
12. Ong HC *et al.* Ethno-medicinal plants used by the Temuan Villagers in Kampung Jeram Kedah, Negeri Sembilan, Malaysia. *Ethno Med* 2011; 5: 95–100.
13. Rahmatullah M *et al.* Ethnomedicinal practices among a minority group of Christians residing in Mirzapur Village of Dinajpur District, Bangladesh. *Adv Nat Appl Sci* 2010; 4: 45–51.
14. Hasan MN *et al.* Medicinal Plants used in Treatment of Tumors: Results from a Survey of Folk Medicinal Practitioners in two Randomly Selected Villages in Khulna and Bagerhat Districts, Bangladesh. In: International Conference on Green Chemistry for Sustainable Development, 2012.
15. Takayama H *et al.* Indole Alkaloids from Tabernaemontana corymbosa in Thailand. *Nat Med Note* 1998; 6: 996.
16. Van Beek TA *et al.* Tabernaemontana L. (Apocynaceae): a review of its taxonomy, phytochemistry, ethnobotany and pharmacology. *J Ethnopharmacol* 1984; 10: 1–156.
17. Rizwana JN *et al.* A survey on phytochemical and bioactivity of plant extracts from Malaysian forest reserves. *J Med Plant Res* 2010; 4: 203–210.
18. Zulkefli HN *et al.* Antioxidant activity of methanol extract of tinospora crispa and Tabernaemontana corymbosa. *Sains Malays* 2013; 42: 697–706.
19. Taher M *et al.* Cytotoxic and Antimicrobial Activities of Alkaloids from Tabernaemontana corymbosa. 5th AASP Conf 2011: 549.
20. Alen Y *et al.* Antinematodal activity of some tropical rainforest plants against the pinewood nematode Bursaphelenchus xylophilus. *Z Naturforsch C* 2000; 55: 295–299.
21. Das SK, Chowdhury SA. Cytotoxic, Anthelmintic and Analgesic activities of methanol extracts from different plant parts of Tabernaemontana Corymbosa (Family: Apocynaceae). *Int J Life Sci Eng* 2015; 1: 202–206.

22. Nge C *et al.* Criofolinine and vernavosine, new pentacyclic indole alkaloids incorporating pyrroloazepine and pyridopyrimidine moieties derived from a common yohimbine precursor. *Org Lett* 2014; 16: 6330–6333.
23. Guo L-L *et al.* A new monoterpenoid indole alkaloid from Ervatamia chinensis. *Chin J Nat Med* 2012; 10: 226–229.
24. Chiou WF *et al.* The mechanism of the vasodilator effect of rutaecarpine, an alkaloid isolated from Evodia rutaecarpa. *Eur J Pharmacol* 1994; 257: 59–66.
25. Lim K-H *et al.* Jerantinines A-G, cytotoxic Aspidosperma alkaloids from Tabernaemontana corymbosa. *J Nat Prod* 2008; 71: 1591–1594.
26. Lim K-H *et al.* Conolutinine, a hexacyclic indole alkaloid with a novel ring system incorporating a diazaspiro center and fused oxadiazepine–tetrahydrofuran rings. *Tetrahedron Lett* 2009; 50: 752–754.
27. Kam T *et al.* Conodiparines A-D, new bisindoles from Tabernaemontana. Reversal of vincristine-resistance with cultured cells. *Bioorg Med Chem Lett* 1998; 8: 1693–1696.
28. Low Y-Y *et al.* Structure, biological activity, and a biomimetic partial synthesis of the lirofolines, novel pentacylic indole alkaloids from Tabernaemontana. *Tetrahedron Lett* 2010; 51: 269–272.
29. Norhayati I *et al. In vitro* antitrypanosomal activity of Malaysian plants. *J Trop For Sci* 2013; 25: 52–59.
30. Raja V *et al.* Novel antitumour indole alkaloid, Jerantinine A, evokes potent G2/M cell cycle arrest targeting microtubules. *Invest New Drugs* 2014; 32: 1–13.
31. Kam T, Pang H. Biologically active ibogan and vallesamine derivatives from Tabernaemontana divaricata. *Chem Biodivers* 2004; 1: 646–656.
32. Nayeem N *et al.* Phytochemical analysis of the leaves of Tabernaemontana Corymbosa using HPLC. *Asian J Chem Pharm Res* 2014; 2: 124–126.
33. Kam T-S, Loh K-Y. 5–00–19,20-dehydroervatamine from leaves of tabernaemontana corymbosa. *Phytochemistry* 1993; 32: 1357–1358.
34. Kam T-S *et al.* Tronoharine, a novel hexacyclic indole alkaloid from a Malayan Tabernaemontana. *Tetrahedron Lett* 1999; 40: 5409–5412.
35. Kam T-S, Sim K-M. Dippinine A, a new alkaloid of the chippiinetype from a Malayan Tabernaemontana. *Nat Prod Lett* 1999; 13: 143–146.
36. Kam T, Sim K. Dippinine C, a new hexacyclic chippiine derivative from Malayan Tabernaemontana. *Heterocycles* 1999; 51: 345–348.
37. Kam TS *et al.* Tronocarpine, a novel pentacyclic indole incorporating a seven-membered lactam moiety. *Tetrahedron Lett* 2000; 41: 2733–2736.
38. Kam T-S *et al.* Voastrictine, a novel pentacyclic quinolinic alkaloid from Tabernaemontana. *Tetrahedron Lett* 2001; 42: 4721–4723.
39. Kam T, Sim K. Dippinines A-D, new iboga-derived indole alkaloids from Tabernaemontana. *Heterocycles* 2001; 55: 2405–2412.
40. Kam T-S, Sim K-M. New tabernamine derivatives from Tabernaemontana. *Heterocycles* 2002; 57: 2137–2143.
41. Lim K *et al.* Four tetracyclic oxindole alkaloids and a taberpsychine derivative from a Malayan Tabernaemontana. *Phytochemistry* 2009; 70: 1182–1186.
42. Lim K-H *et al.* Seco-tabersonine alkaloids from Tabernaemontana corymbosa. *Phytochemistry* 2009; 70: 424–429.
43. Lim K-H, Kam T-S. Conoliferine and isoconoliferine, structurally novel alkaloid-lignan conjugates from Tabernaemontana corymbosa. *Tetrahedron Lett* 2009; 50: 3756–3759.
44. Lim K-H, Kam T-S. Conomicidines A and B, unusual alkaloid-hydroxycinnamyl alcohol conjugates from Tabernaemontana corymbosa. *Helv Chim Acta* 2009; 92: 1895–1902.
45. Kam T-S, Sim K-M. Vobasonidine and vobatricine, novel bisindole alkaloids from a Malayan Tabernaemontana. *Helv Chim Acta* 2002; 85: 1027.
46. Bergman PJ. Mechanisms of anticancer drug resistance. *Vet Clin North Am Small Anim Pract* 2003; 33: 651–667.
47. Krishna R, Mayer LD. Multidrug resistance (MDR) in cancer. Mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs. *Eur J Pharm Sci* 2000; 11: 265–283.
48. Frei R *et al.* Total synthesis and biological evaluation of jerantinine E. *Angew Chem Int Ed Engl* 2013; 52: 13373–13376.
49. Qazzaz ME *et al. In vitro* anticancer properties and biological evaluation of novel natural alkaloid jerantinine B. *Cancer Lett* 2016; 370: 185–197.
50. Kohno K *et al.* Vincristine-resistant human cancer KB cell line and increased expression of multidrug-resistance gene. *Jpn J Cancer Res* 1988; 79: 1238–1246.
51. Rautio J *et al.* Prodrugs: design and clinical applications. *Nat Rev Drug Discov* 2008; 7: 255–270.
52. Perez EA. Microtubule inhibitors: differentiating tubulin-inhibiting agents based on mechanisms of action, clinical activity, and resistance. *Mol Cancer Ther* 2009; 8: 2086–2095.
53. Kam T-S *et al.* Cytotoxic effects and reversal of multidrug resistance by ibogan and related indole alkaloids. *Bioorg Med Chem Lett* 2004; 14: 4487–4489.
54. Ryan BM *et al.* Survivin: a new target for anti-cancer therapy. *Cancer Treat Rev* 2009; 35: 553–562.
55. Miao W *et al.* Safety and tumor tissue accumulation of pegylated graphene oxide nanosheets for co-delivery of anticancer drug and photosensitizer. *Biomaterials* 2013; 34: 3402–3410.
56. Muthoosamy K *et al.* Exceedingly biocompatible and thin-layered reduced graphene oxide nanosheets using an eco-friendly mushroom extract strategy. *Int J Nanomedicine* 2015; 10: 1505–1519.
57. Nge CE *et al.* Voatinggine and tabertinggine, pentacyclic indole alkaloids derived from an iboga precursor via a common cleavamine-type intermediate. *Org Lett* 2013; 15: 4774–4777.

58. Ma K *et al.* Tabercarpamines A-J, apoptosis-inducing indole alkaloids from the leaves of Tabernaemontana corymbosa. *J Nat Prod* 2014; 77: 1156–1163.
59. Ma K *et al.* Bistabercarpamines A and B, first vobasinyl-chippiine-type bisindole alkaloid from Tabernaemontana corymbosa. *Tetrahedron Lett* 2014; 55: 101–104.
60. Guo LL *et al.* Indole alkaloids from Ervatamia chinensis. *Phytochemistry* 2012; 74: 140–145.
61. Sim DS-Y *et al.* Cytotoxic vobasine, tacaman, and corynanthe-tryptamine bisindole alkaloids from Tabernaemontana and structure revision of tronoharine. *J Nat Prod* 2014; 77: 2504–2512.
62. Zhang Y *et al.* New vobasinyl-ibogan type bisindole alkaloids from Tabernaemontana corymbosa. *Fitoterapia* 2015; 100: 150–155.