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Phytochemical Survey and Pharmacological Activities of the Indole Alkaloids in the Genus *Voacanga* Thouars (Apocynaceae) – An Update

Allan Patrick G. Macabeo,[1,3*] Grecebio Jonathan D. Alejandro[2], Arnold V. Hallare[4], Warren S. Vidar[1], Oliver B. Villaflores[1]

[1]Phytochemistry and [2]Plant Sciences, Research Center for the Natural Sciences, University of Santo Tomas, Espana Blvd, Manila 1015 Philippines
[3]Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, D-93053 Regensburg, Germany
[4]Department of Biology, CAS, University of the Philippines-Manila, Padre Faura St., Manila 1000 Philippines
**Corresponding author: Phone: +499419434631*
E-mail: allan-patrick.macabeo@chemie.uni-regensburg.de/allanpatrick_m@yahoo.com

ABSTRACT
Numerous species of the Apocynaceous genus *Voacanga* Thouars have been demonstrated to elaborate a host of indole alkaloids that display various structural complexities and a wide array of biological activities. Monoterpenoid indole alkaloids are nitrogenous metabolites borne from the biosynthetic union of tryptophan and the terpene-derived iridoid, secologanin. As a genus is closely related to *Tabernaemontana*, representative species of *Voacanga* were reported to contain the vobasine, vallesamine, eburnane, iboga and aspidosperma–type indole alkaloids. A lot of these compounds are associated with analgesic, CNS, antimicrobial, anti-ulcer, cytotoxic, antioxidant and antimalarial activities. *Voacanga* is a small taxon with 12 species that are mainly found in tropical Africa and Malesia except for *V. grandifolia* which extends to Australia. This comprehensive review compiles the phytochemical and pharmacological explorations that have been undertaken on *Voacanga* in relation to its indole alkaloids.

KEY WORDS
Voacanga, indole alkaloids, anti-ulcer, antibacterial, cytotoxic, CNS activity

INTRODUCTION

Several plant-derived drugs and active principles have continued to serve as promising phytotherapeutic agents and as model inspirations for molecular drug design. From a vast number of compounds unearthed in several plant species, the monoterpenoid indole alkaloids boasts a myriad of chemical and biological studies rooting from its display of molecular complexities and wide range of antagonistic activities against human-related diseases such as cancer, cardiovascular diseases and infections. They are one of the largest groups of plant bases known today comprised of over 2000 structures (1). Their abundance is well-identified in plant species such as those belonging to the family Apocynaceae i.e. *Vinca, Alstonia, Rauvolfia, Voacanga, Tabernaemontana,* and *Strychnos*. Other plant families known to have these metabolites are Rubiaceae, Logniaceae, Rutaceae and Nyssaceae (2). The biosynthetic pathways leading to several classes of terpene-based indole alkaloids are well-documented (1-3).

The *Voacanga* Thouars, belonging to the family Apocynaceae [subfam. Rauvolfioideae, tribe Tabernaemontaneae] (4), is a small taxon comprising 12 species sensu Leeuwenberg (5) and Middleton (6). The genus is mainly distributed in tropical Africa (e.g., Zambia, Zimbabwe, Malawi, Mozambique) with 7 spp., followed by Malesia (Sumatra, Java, Sulawesi, Borneo, Philippines, Lesser Sunda Islands, Moluccas, New Guinea) with 5 spp. One Malesian species, the *Voacanga grandifolia* (Miq.) Rolfe, extends to Queensland, Australia (5).

As a contribution to the wealthy and fast growing literature concerning indole alkaloids identified in several Apocynaceae flora, this review provides a comprehensive update regarding phytochemical and pharmacological studies done on this class of secondary metabolites from *Voacanga species*.

Botanical description

Voacanga species are generally shrubs or trees, dichotomously branched, with white latex and terete branches which are mostly sulcate when dry. Leaves opposite, with colleters in the axils, the bases of petioles connate forming a short ocrea; blade usually elliptic or obovate, cuneate at base. Inflorescences cyme or with solitary flower, long-pedunculate, usually lax, with 2 inflorescences at each ramification, the bracts deciduous or persistent. Flowers actinomorphic, fragrant; calyx green, campanulate to cylindrical, usually with a distinct connate tube, lobes free, with colleters inside; corolla lobes mostly creamy or yellow, sinistrose, spreading or recurved, the tubes narrow or trumpet-shaped, short or slightly longer than the calyx. Stamens subsessile, included or semi-exserted; anthers narrowly triangular, sagittate at base, acuminate at the sterile apex, glabrous, introrse, weakly attached to the style head. Disk adnate to sides of carpels. Gynoecium glabrous, with 2 carpels, apocarpous but apically united into a common style; ovary mostly broadly ovoid; style filiform, thickened at the apex, the stigma short. Fruit creamy or yellow, follicle, paired, somewhat united at the base. Seeds covered in a fleshy aril, numerous, large, obliquely ellipsoid or reniform; endosperm creamy to white, starchy and ruminate (4-5).

The African *Voacanga* species (e.g., *V. africana* and *V. thouarsii*)

are widespread, extending up to 20-25 m high in open woodland or light forest, riverine forests or in moist places of evergreen forest and savannas. *Voacanga africana* has acuminate leaves, sometimes acute or obtuse, papery when dry; calyx lobes mostly partly recurved, longer than the tubes; and corolla lobes obovate or elliptic. On the other hand, *V. thouarsii* is characterized by rounded or obtuse leaves, thickly coriaceous; calyx clasping the corolla, barrel-shaped to cylindrical; and corolla lobes broadly obcordate (4).

Malesian species of *Voacanga* (e.g., *V. foetida* and *V. grandifolia*) grow up to 15-20 m high, in open forest or scrub. The calyx tubes of both *V. foetida* and *V. grandifolia* are not clasping the corolla tube and their corolla lobe apices are either rounded or emarginate (5). *Voacanga foetida* has a long corolla tube (28-45 mm) and calyx tube (14-40 mm) while *V. grandifolia* is distinct by a smaller corolla tube (9-24 mm) and calyx tube (10-20 mm).

The Philippine indigenous *Voacanga* species (*V. megacarpa* and *V. globosa*) are trees, up to 15-25 m high, in secondary forest or scrub. Both *V. megacarpa* and *V. globosa* are characterized with white corolla and the stamens are inserted. The calyces of *V. megacarpa* are almost free and the lobes much longer than the tube while *V. globosa* have connate with lobes shorter than the tube. In addition, the corolla lobes are elliptic, rounded to emarginated at apex and the tubes 22-40 mm long in *V. megacarpa* while elliptic to obovate, acute to obtuse at apex and the tubes 24-50 mm long in *V. globosa* (5).

Ethnopharmacology

Among the species of *Voacanga*, *V. africana* Stapf. is considered to be the most popular for folk herbal medicine. The extracts of this plant is used by the Africans for various ethnomedical practices such as treatment for leprosy, diarrhea, generalized edema, convulsions and madness figures (7). They also use them for curing orchitis, ectopic testes as well as gonorrhea (8). *Voacanga brateata* Stapf. is reported to be used by common folks as stimulants in Gabon, West Africa for them to become high (9). In addition, scrapings from the inner bark layer of *V. grandifolia* are rubbed on to the skin as a medication for dermatitis (TM) in Riau Province, Sumatra, Indonesia (10). *Voacanga foetida* (Blume) Rolfe. locally called '*kumbi*', a species mainly distributed in Lombok, Indonesia is also well-known for the treatment of various ailments. The aqueous extract of the leaves or bark is used commonly to treat a wide range of skin conditions such as wounds, itches, and swellings (11-12).

Other Uses

Africans believe that if the fruits and leaves of *V. africana* are hung over a house-door, witches will be drawn away. Its fruit is considered to be poisonous and its bark is also used as an arrow poison (13). The African Magic Healers keep *V. africana* as one of their well-guarded secrets. There is a little knowledge though concerning on its actual utilization except that its preparations are used as a medium for ritual and visionary purposes. It was documented that some magicians make an intake of 50 seeds to improve visionary abilities. Its latex is used as a rubber adulterant (14).

The *Voacanga* Indole Alkaloids

A number of old phytochemical literatures are available for the indole alkaloids of *Voacanga*. It has been shown in many species that these secondary metabolites are highly localized in the different parts of the plant such as the leaves, roots, stem, branch, and seeds. It has to be noted that earlier studies pertaining to *V. dregei* alkaloids have been included under *V. thouarsii* due to botanical revision.

Biosynthetic formation. The monoterpenoid indole alkaloids are biosynthetically made from tryptophan and secologanin, a terpene iridoid. It is believed that the corynanthe alkaloids are the precursor anabolites for the more structurally complex aspidosperma, iboga, and strychnos alkaloid (15). Preakuammicine (a strychnos-type intermediate and a strictosidine derivative) is the common precursor of the aspidosperma, strychnos and iboga alkaloids. Stemmadenine undergoes a rearrangement reaction to afford dehydrosecodine, an acrylic ester intermediate, which serves as a common precursor for the aspidosperma and the iboga structures (16-18). It has not been verified through biosynthetic experiments that the iboga alkaloid, catharanthine, and the aspidosperma alkaloid, tabersonine, are produced by way of Diels–Alder reaction of dehydrosecodine (1).

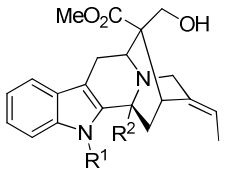
Table 1 : The monoterpenoid indole alkaloids from Voacanga Thouars

Indole Alkaloid	Classification	Source
16-*Epi*-voacarpine [**1**]	corynanthe	*V. chalotiana* (19)
17-*O*-acetyl-19, 20-dihydrovoachalotine [**2**]	corynanthe	*V. chalotiana* (20)
18'-Decarbomethoxyvoacamine [**3**]	iboga-vobasine	*V. africana* (21), *V. thouarsii* (22)
2'-Deoxyvobtusine [**4**]	aspidosperma-aspidosperma	*V. africana* (23-24)
2'-Deoxyvobtusine lactone [**5**]	aspidosperma-aspidosperma	*V. africana* (23-24)
3-Hydroxyvoachalotine [**6**]	corynanthe	*V. chalotiana* (25-27)
20'- Hydroxyvoacamidine [**7**]	iboga-vobasine	*V. africana* Geigy (28)
3,6-Oxidovoacangine [**8**]	iboga	*V. schweinfurthii* (29)
3ε-Hydroxyvobtusine [**9**]	aspidosperma-aspidosperma	*V. chalotiana* (30)
Akuammidine [**10**]	corynanthe	*V. chalotiana* (27), *V. grandifolia* (31)
Amataine or subsessiline [**11**]	aspidosperma-aspidosperma	*V. chalotiana* (25); *V. thouarsii* (32)
Beninine [**12**]	aspidosperma	*V. africana* (33), *V. chalotiana* (25)
Coronaridine [**13**]	iboga	*V. schweinfurthii* (29)
Cuanzine [**14**]	eburnane	*V. chalotiana* (25)

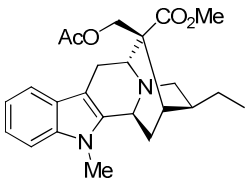
Decarbomethoxyapocuanzine [**15**]	eburnane	*V. chalotiana* (25)
Dehydrovoachalotine [**16**]	corynanthe	*V. chalotiana* (25)
Desacetylvindoline [**17**]	aspidosperma	*V. grandifolia* (34)
Dregamine [**18**]	vobasine	*V. thouarsii* (35)
Epivoacangarine [**19**]	iboga	*V. bracteata* (36)
Epivoacorine [**20**]	iboga-vobasine	*V. bracteata* (36)
Folicangine [**21**]	aspidosperma-aspidosperma	*V. africana* (37)
Ibogaine [**22**]	iboga	*V. schweinfurthii* (29), *V. thouarsii* (32)
Iboluteine [**23**]	iboga	*V. thouarsii* (22)
Isovoafoline [**24**]	aspidosperma-aspidosperma	*V. africana* (24)
Lochnericine [**25**]	aspidosperma	*V. africana* (38)
Lombine [**26**]	corynanthe	*V. foetida* (39)
Minovincine [**27**]	aspidosperma	*V. africana* (38)
O-methyl-16-*epi*-Δ^{14}-vincanol [**28**]	eburnane	*V. africana* (40)
Perivine [**29**]	corynanthe	*V. schweinfurthii* (28)
Polyneuridine [**30**]	corynanthe	*V. chalotiana* (27)
Quimbeline [**31**]	aspidosperma-aspidosperma	*V. chalotiana* (41)
Subsessiline lactone [**32**]	aspidosperma-aspidosperma	*V. thouarsii* (37)
Tabernaemontanine [**33**]	vobasine	*V. globosa* (42)
Tabersonine [**34**]	aspidosperma	*V. africana* (43), *V. schweinfurthii* (29), *V. thouarsii* (22)
Tetrahydroalstonine [**35**]	corynanthe	*V. chalotiana* (25)
Voacafricine*	-	*V. africana* (44)
Voacafrine [**36**]	vobasine	*V. africana* (44)
Voacamidine [**37**]	iboga-vobasine	*V. africana* (45), *V. schweinfurthii* (29)
Voacamine [**38**]	iboga-vobasine	*V. africana* (46), *V. papuana* (47), *V. megacarpa* (48), *V. globosa* (49),*V. schweinfurthii* (50), *V. thouarsii* (22)
Voacamine N-oxide [**39**]	iboga-vobasine	*V. africana* (51)
Voacangine [**40**]	iboga	*V. africana* (46), *V. globosa* (49), *V. foetida* (39), *V. schweinfurthii* (50), *V. thouarsii* (32,52)
Voacangine hydroxyindolenine [**41**]	iboga	*V. africana* (21)
Voachalotine [**42**]	corynanthe	*V. chalotiana* (53)
Voachalotine oxindole [**43**]	corynanthe	*V. chalotiana* (30)
Voacinol [**44**]	aspidosperma-aspidosperma	*V. grandifolia* (34)
Voacoline [**45**]	corynanthe	*V. chalotiana* (54)
Voacorine [**46**]	iboga-vobasine	*V. africana* (55), *V. chalotiana* (56)
Voacristine [**47**]	iboga	*V. africana* (45), *V. thouarsii* (32)
Voacryptine [**48**]	iboga	*V. africana* (57)
Voafolidine [**49**]	aspidosperma-aspidosperma	*V. africana* (58)
Voafoline [**50**]	aspidosperma-aspidosperma	*V. africana* (24)
Voafrine A [**51**]	aspidosperma-aspidosperma	*V. africana* (59)
Voafrine B [**52**]	aspidosperma-aspidosperma	*V. africana* (59)
Voaluteine [**53**]	iboga	*V. thouarsii* (22)
Voamonine [**54**]	corynanthe	*V. chalotiana* (19)
Voaphylline [**55**]	vallesamine	*V. africana* (60)
Voaphylline hydroxyindolenine [**56**]	vallesamine	*V. africana* (61)
Vobasine [**57**]	vobasine	*V. africana* (57), *V. schweinfurthii* (29), *V. thouarsii* (22)
Vobasinol [**58**]	vobasine	*V. schweinfurthii* (29)
Vobtusamine [**59**]	eburnane -aspidosperma	*V. chalotiana* (62)
Vobtusine [**60**]	aspidosperma-aspidosperma	*V. africana* (46), *V. chalotiana* (25), *V. papuana* (47), *V. megacarpa* (48), *V. globosa* (63), *V. schweinfurthii* (50), *V.*

		thouarsii (32,52)
Vobtusine 3-lactam [**61**]	aspidosperma-aspidosperma	*V. thouarsii* (32,52)
Vobtusine 3-lactam N_b'-oxide [**62**]	aspidosperma-aspidosperma	*V. thouarsii* (32,52)
Vobtusine lactone [**63**]	aspidosperma-aspidosperma	*V. africana* (24), *V. thouarsii* (32)
Δ^{14}-Vincamine [**64**]	eburnane	*V. chalotiana* (25)
Δ^{14}-Vincamone [**65**]	eburnane	*V. africana* (40)
Δ^{14}-Vincanol [**66**]	eburnane	*V. africana* (40)

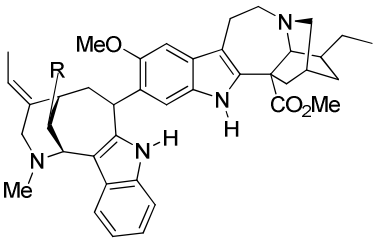
*no structure was assigned for this compound (44). However, it was hypothesized that it has an analogous structure with vincadiffine (64).



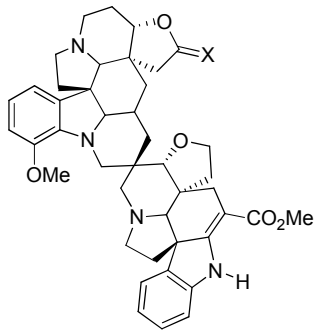
R^1= H, R^2=OH, 16-epi-voacarpine **[1]**
R^1= Me, R^2=OH, 3-hydroxyvoachalotine **[6]**
R^1= H, R^2=H, akuammidine **[10]**
R^1= Me, R^2=H, voachalotine **[42]**



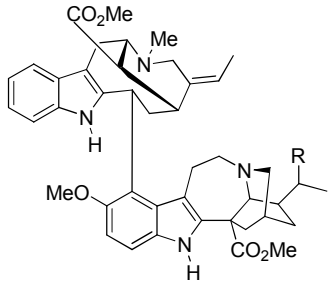
17-O-acetyl-19,20-dihydrovoachalotine **[2]**



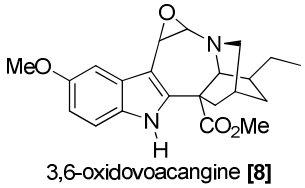
R =H, 18'-decarbomethoxyvoacamine **[3]**
=CO_2Me, voacamine **[38]**



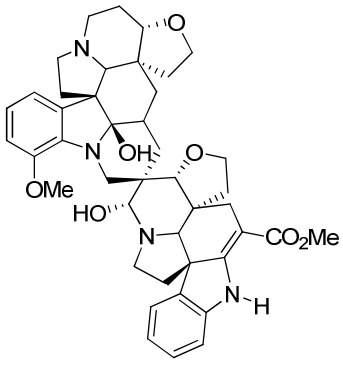
R= H_2, 2'-deoxyvobtusine **[4]**
= O, 2'-deoxyvobtusine lactone **[5]**



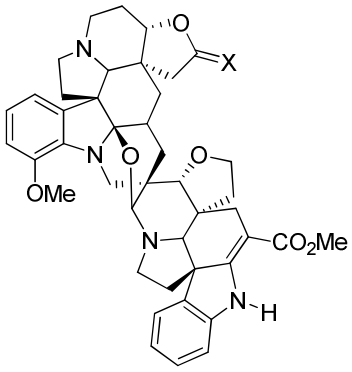
R =OH, 20'-hydroxyvoacamidine **[7]**
=H, voacamidine **[37]**



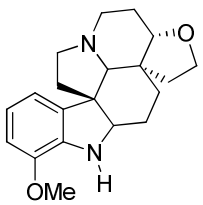
3,6-oxidovoacangine **[8]**



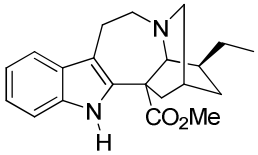
3-hydroxyvobtusine **[9]**



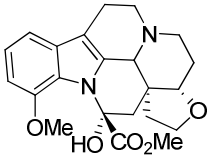
X=H_2, amataine or subsessiline **[11]**
X=O, subsessiline lactone **[32]**



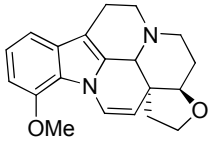
beninine **[12]**



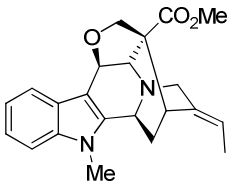
coronaridine
[13]

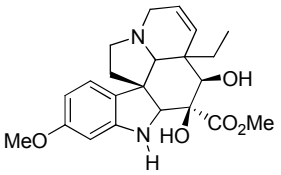


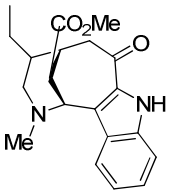
cuanzine **[14]**

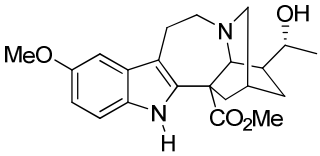


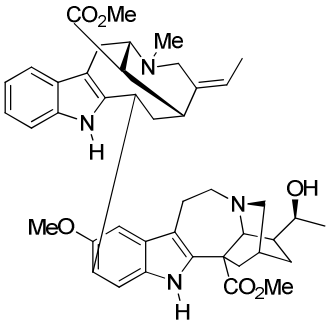
decarbomethoxyapocuanzine **[15]**

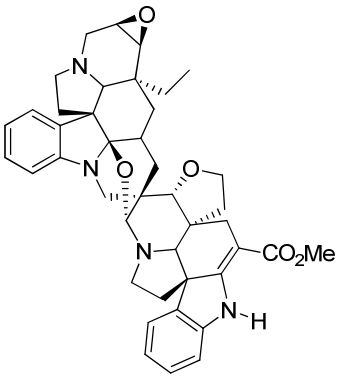

dehydrovoachalotine **[16]**

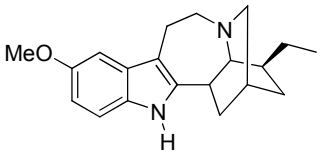

desacetylvindoline **[17]**

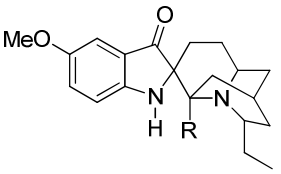

dregamine **[18]**

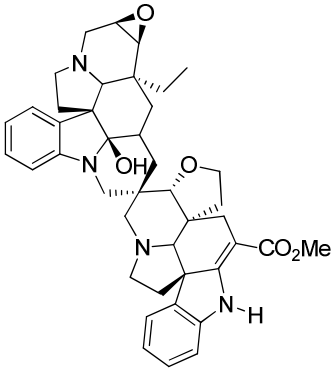

epivoacangarine **[19]**

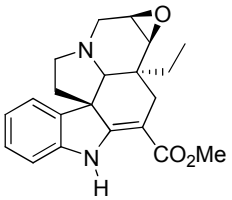

epivoacorine **[20]**

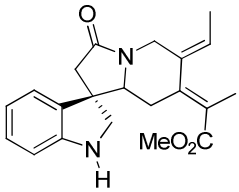

folicangine **[21]**

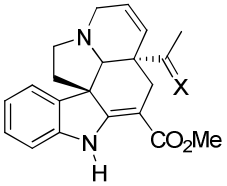

ibogaine **[22]**

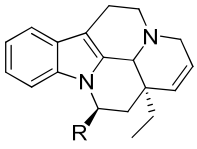

R= H,iboluteine **[23]**
= CO_2Me, voaluteine **[53]**

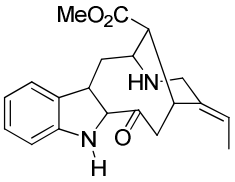

isovoafoline **[24]**

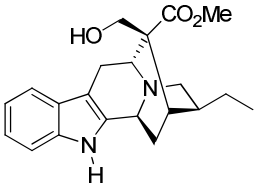

lochnericine **[25]**

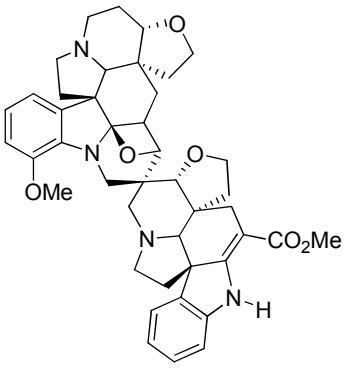

lombine **[26]**


X = O, minovincine **[27]**
= H_2, tabersonine **[34]**

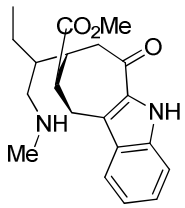

R = OMe, O-methyl-16-epi-delta 14-vincanol **[28]**
= H, delta 14-vincamone **[65]**
= OH, delta 14-vincanol **[66]**


perivine **[29]**

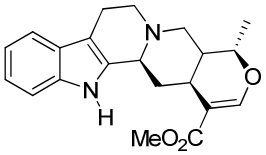

polyneuridine **[30]**



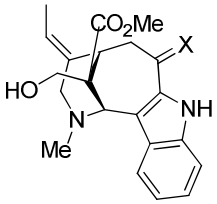
quimbeline **[30]**



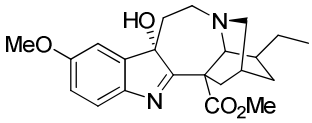
tabernamontanine **[33]**



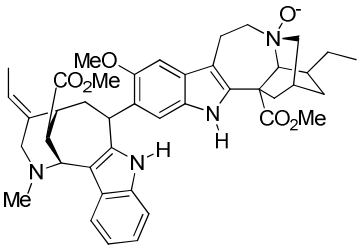
tetrahydroalstonine **[35]**



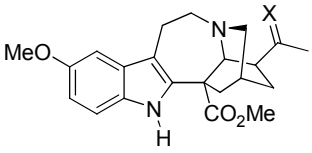
voacafrine **[36]**



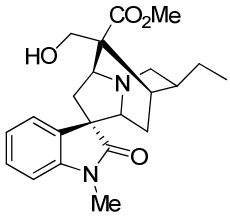
voacangine hydroxyindolenine **[41]**



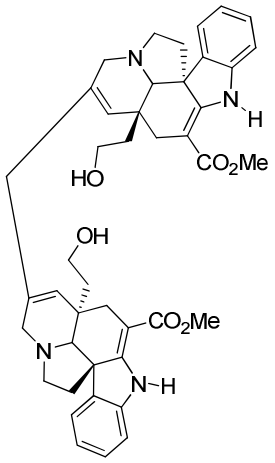
voacamine N-oxide **[39]**



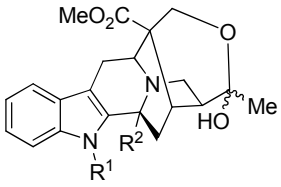
X =H_2, voacangine **[40]**
=H,OH, voacristine **[47]**
=O, voacryptine **[48]**



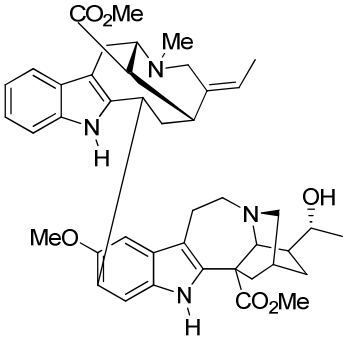
voachalotine oxindole **[43]**



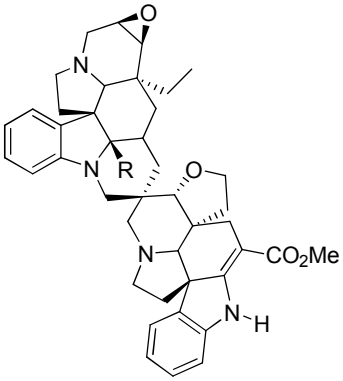
voacinol **[44]**



voacoline **[45]**



voacorine **[46]**



R =OH, voafolidine **[49]**
= H, voafoline **[50]**

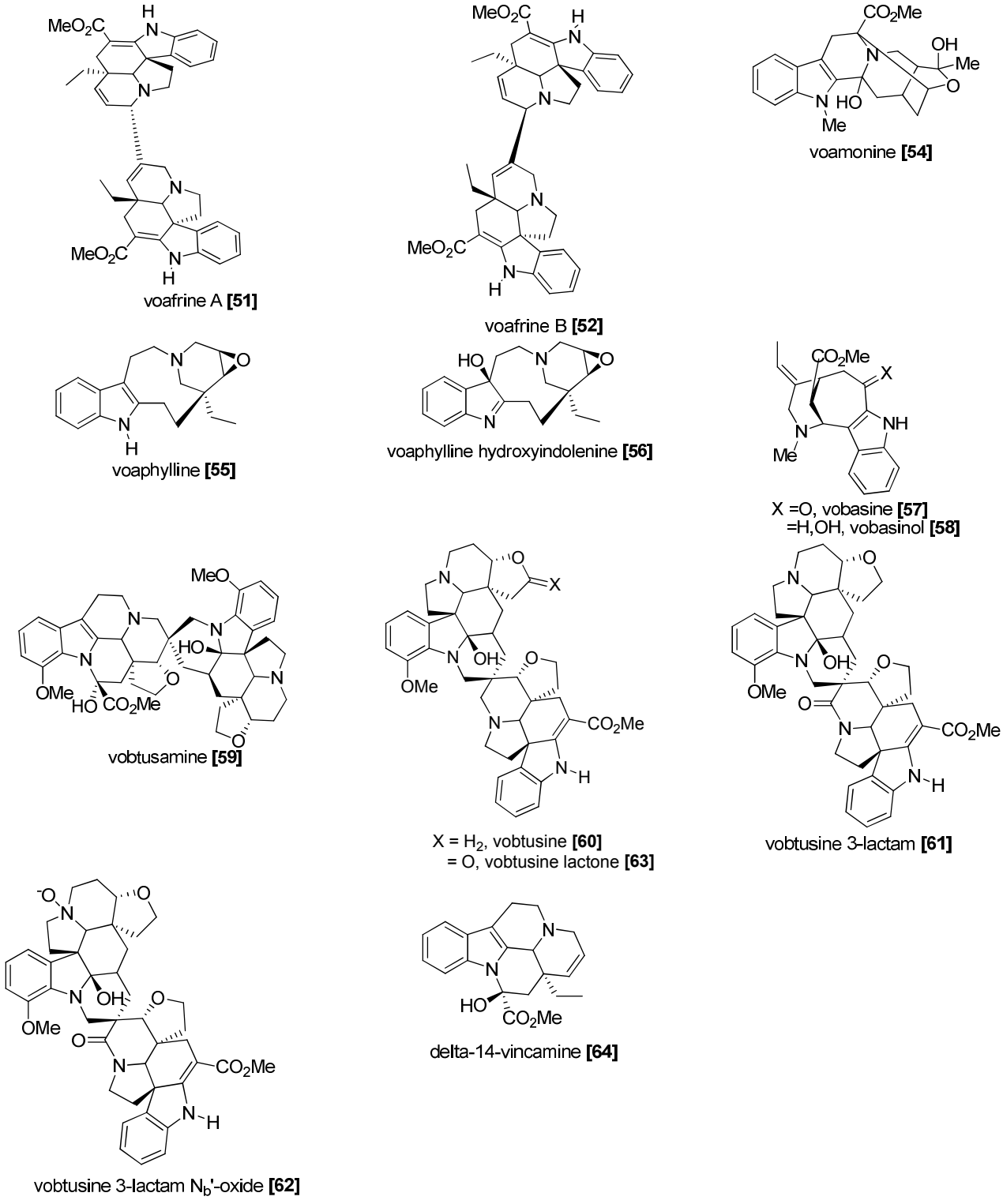


Figure 1 : The monoterpenoid indole alkaloids from Voacanga Thouars.

Pharmacological Properties

Studies on the biological effects of *Voacanga* have identified several indole alkaloids as the major active phytoconstituents. The following list down several pharmacological researches done on these *Voacanga* metabolites.

Effects on the Cardiovascular System. Studies on the pharmacological activity of *V. africana* began in the early 1950s when the roots of this African shrub yielded voacanginine (voacamine) **[38]** and voacangine **[40]**. The mode of action of the isolates was similar to that of digitalin. However, a previous study using isolated rabbit auricle revealed that both compounds exhibited toxicity of about one-third of that of digitalin (65). Moreover, another alkaloid voacaline (voacorine) **[46]** was isolated and showed similar cardiotonic properties (66).

The pharmacodynamic activity of the camphorsulfonate derivative of **38** was compared with its sulfate salt. The intravenous LD_{50} of both alkaloidal salts in mice was 46.2 and 21.5 mg/kg by weight. Voacamine camphorsulfonate was proven to have a myotonic effect without coronary vasodilation using an *in vivo* perfusion of isolated rabbit auricle. Moreover, this salt was found to be hypotensive and has no hypothermic effect but was antipyretic in several experimental animals and reduced the convulsive effect of high insulin doses. It also exhibited a parasympathomimetic and sympatholytic effect (67).

In addition, cuanzine **[14]** from *V. chalotiana* was observed to be capable of vasodilating activity like vincamine **[64]** and its derivatives, using ethyl apovincaminate as the standard. The said reference drug is used in the management of cerebral and peripheric vascular disorders. In a study aimed to investigate the cerebral antihypoxic activity of **14** (IdB 1119) and some of its semisynthetic derivatives: apocuanzine (IdB 1057), apocuanzine *N*-oxide (IdB 1116), 9-bromoapocuanzine (IdB 1117) and the 16-keto derivative (IdB 1118), it was found that cuanzine and its derivatives showed a significant antihypoxic vincamine-like activity. Among them, IdB 1057 posed as the most interesting compound being about twice as potent as ethyl apovincaminate (68).

Effects on the Central Nervous System. *Voacanga africana* contains ibogaine **[22]**, a powerful hallucinogenic compound (69). Kombian and co-workers, reported that this natural alkaloid is effective in the treatment of withdrawal syndrome and craving among drug dependents. Using a nystatin perforated patch-recorded technique, the mechanistic mode of action of ibogaine has been linked to the modulation of the neuronal excitability and synaptic transmission in the parabrachial nucleus. Modulation takes effect by depolarizing parabrachial neurons with increasing excitability and firing rate; by depression of the non-NMDA receptor-mediated fast synaptic transmission; and lastly, by involvement of dopamine receptor activation for its actions (70).

Gastro-intestinal protective activity. The aqueous bark extract of *V. africana* which may potentially contain polar alkaloids, was reported to have gastro-protective effects compared to its HCl/ethanol extract. The aqueous extract was also found to prevent gastric mucosal damage though it did not significantly reduce the acidity of the gastric juice (71). This result suggests that the protective effect offered by the extract is not due to simple neutralization of the hydrochloric acid in the solution but rather through increased mucous defenses or through the reduction of the proteolytic activity of the pepsin in the gastric juice (72). In a separate study, it was reported that *V. africana* extracts can be used for treating of intestinal diseases (73) caused by *Entamoeba histolytica* with an MIC = 62.5 ug/mL. In addition, organisms such as *Campylobacter jejuni* and *C. coli* were found to be susceptible to *V. africana* extract (71).

The alkaloid TN (structure unknown) from *V. africana* was assayed for cytoprotective, anti-secretory and ulcer healing actions. Through oral administration, the compound prevented dose-dependent ulcer formation induced by HCl/ethanol at 36-75%, absolute ethanol at 43-75%, HCl-ethanol/indomethacin at 58-84%, Pylorus ligation at 31-100%, cold restraint stress at 68-100% and histamine at 49-100%. This alkaloid also decreased the Shay-ligated gastric acid secretion. TN has gastric anti-secretory effects similar to histamine receptor blockers. Moreover, its cytoprotective and ulcer healing effects are associated to its property to strengthen gastric mucosal defenses via increased gastric mucus production (74). When combined with ranitidine, a synergistic anti-secretory effect was observed (75).

Anti-cancer activity. Amataine **[11]** from *V. africana* together with other indole alkaloids from *Tabernaemontana elegans* showed remarkable cytotoxic activity when tested against VERO cells (76). Cytotoxicity measurements were done using Frame Kenacid Blue method for protein, Neutral Red for lysosomes and Crystal Violet method for the nucleus. The compound exhibited an ID_{50} of 5 μg/mL, 3 μg/mL and 3 μg/mL, respectively, based on the bioassay results of the three cytotoxicity methods mentioned. Using optical microscopy tests, the inhibition of the cell culture proliferation with pycnotic cells and clear vacuolization were qualitatively observed.

Antibacterial and antimycobacterial Property. The crude alkaloid extracts of *V. foetida* bark were observed to inhibit the hydrolysis of FDA by bacteria at a test concentration of 5 mg/ml. Moreover, this extract also inhibited the growth of *Staphylococcus aureus*, and *Escherichia coli*, at a 5 mg/ml against test concentration. Bioassay-guided isolation afforded the new compound lombine **[26]** to be the active antibacterial principle. The antibacterial activity of this compound was found to be greater than the crude extract, with 100% inhibition at 0.5 mg/ml for both bacteria. The other alkaloid voacangine **[40]** showed bacteriostatic activity against *S. aureus,* killing 87% of the bacterial cells at a concentration of 1.0 mg/ml (11-12).

In an Italian patent, a pharmaceutical preparation from *V. africana* was made for the treatment of *Mycobacterium ulcerans* (77). In a separate study, alkaloid **40** was found to possess a pronounced activity against three species of *Mycobacterium* namely *tuberculosis, avium and kansasii*. Corresponding Bactec versus 7H11 MICs (mg ml^{-1}) of these compounds against *M. tuberculosis, M. avium, and M. kansasii* were, respectively, 50, 50,

100 versus 50, s200, 100 (78).

Antiplasmodial Property. Voacamine **[38]**, an iboga-vobasine type alkaloid, was reported by Federici and co-workers (79) to exhibit anti-plasmodial activity *in vitro*. A follow-up study was done by the group of Ramanitrahasimbola *et al.* on its *in vivo* anti-malarial activity. In this study, compound **38** showed significant anti-malarial activity. However, its activity is less pronounced compared to the reference compound chloroquine. Using a synchronized culture, it was also observed that this alkaloid acted specifically on the trophozoite and schizont stages of the *Plasmodium falcifarum*, suggesting a potential effect on the nuclear division of the parasite, possibly on the DNA or the protein synthesis (80).

Anti-inflammatory activity. The activity of chlorpromazine, reserpine, and the total alkaloids from *Voacanga africana* (HCl salts) on rat-paw edema caused by egg albumen and dextran was explored for their inhibitory activity on the formation of the edema. It was found for these compounds an ability to increase capillary resistance to run parallel with the edema inhibition (81).

SUMMARY AND CONCLUSION

The present review describes the botanical, phytochemical, and pharmacological aspects of *Voacanga* Thouars (Family Apocynaceae) and summarizes the most interesting findings on the chemical and pharmacologic researches on the various monoterpenoid indole alkaloids elaborated by the member species. Much of the recorded uses of *Voacanga* species in folk herbal medicine have been linked to magic healings, rituals, and for improving visionary abilities. In addition, extracts from member species have also been used for various ethnomedical practices including the treatment for a wide range of skin conditions such as wounds, itches, dermatitis, or leprosy as well as diarrhea, generalized edema, convulsions, orchitis, ectopic testes and gonorrhea. A survey of phytochemical literature shows that the leaves, roots, barks, stems, branches, and seeds of almost all species elaborate the *eburnane*, *iboga, vobasine, vallesamine* and *aspidosperma–type* indole alkaloids. Several purified compounds provide credence to the folkloric, ethnomedical uses of *Voacanga* plants as listed above. Pharmacological studies conducted on the extracts and purified alkaloids of *Voacanga* indicate the immense potential of the member species to be used as analgesic, stimulant, vasodilator, CNS modulator, antimicrobial, antimycobacterial, anti-parasitic, antiplasmodial, anti-ulcer, anti-inflamatory, cytotoxic, antitumor, and anti-malarial agents. However, much additional work is still needed to further validate the above mentioned biological activities of *Voacanga*-derived indole alkaloids. Further research to discover new clinical applications of the phytoconstituents, clinical trials, and product development are also necessary to fully exploit the medicinal potential of *Voacanga* plants not only for the present but for future generations.

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