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Review Article

Chemical Diversity of Indole Alkaloids from Malaysian *Kopsia* Species (Apocynaceae) and Their Biological Activities

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ABSTRACT

The genus *Kopsia*, which belongs to the family Apocynaceae, has been used extensively in traditional treatment. This mini-review provides a comprehensive analysis of the chemical diversity of indole alkaloids from Malaysian *Kopsia* species and their biological activities. Fourteen species with 164 indole alkaloids have already been studied and successfully isolated and characterised. Most of them are categorised as aspidofractinine, aspidospermane and eburnane types. The literature and references for this manuscript were obtained from various sources including SciFinder®, Reaxys®, ScienceDirect®, PubMed Central®, NIH National Library of Medicine, Google Scholar and The Plant List®.

Keywords: Apocynacae, *Kopsia*, indole alkaloids, aspidofractinine, aspidospermane, eburnane

1. INTRODUCTION

The name "*Kopsia*" which belong to Apocynaceae family was published in 1823 by Blume in honour of the Dutch botanist J.Kops (1765-1849) with one species, *K. arborea* Blume. To date, there are about 23 species have been identified from Southern China and Burma to northern Australia and Vanuatu (Middleton, 2004). Most species occur in Southeast Asia, namely in Peninsular Malaysia and Borneo (Middleton, 2004). In Malaysia, there are nearly 14 species which have been particularly well-investigated. Among the Malays, *K. larutensis* King and Gamble are known for its Malay names "pokok karang", *K. macrophylla* Hook. f. as "bangku", *K. pauciflora* Hook f. as "sertong", *K. singapurensis* Ridl. as "selada" and *K. fruticosa* (Roxb.) A.DC. as "cabai hutan". Table 1 compiled all *Kopsia* species found in Peninsular Malaysia and Borneo including its distribution.

The *Kopsia* species has been suggested for various medicinal uses. In 1966, a report by Burkill states that the root of *K. larutensis* King & Gamble, *K. macrophylla* Hook f., *K. singapurensis* Ridl., and *K. pauciflora* Hook f. is used by the Malays for poulticing ulcerated noses in tertiary syphilis. In Java, *K. arborea* is used for headaches. *K. officinalis* Tsiang & Li is used in traditional Chinese medicine to treat rheumatoid arthritis and gout (Sevenet et al., 1994). In addition, *Kopsia* species have also been studied for their biological activities. Chan et al., (2016) reported that *K. dasyrachis* and *K. fruticosa* have anti-plasmodial properties, while *K. arborea, K. singapurensis* and *K. tenuis* have anti-proliferative properties against human cancer cells (Chan et. al., 2016). A positive result on the anti-hypertensive activity was also reported for *K. teoi* from a preliminary screening of its alkaloid extracts.

Table 1. *Kopsia* species and its distribution in Peninsular Malaysia and Borneo

Species	Distribution
K. arborea Blume	Perak
K. dasyrachis Ridl.	Sabah (Lukan)
K. deverrei L. Allorge	Johor
K. fruticosa	Selangor, Federal Territories of Putrajaya
K. larutensis	Perak
K. griffithii King & Gamble	Melaka, Selangor
K. macrophylla Hook. F	Negeri Sembilan, Johor (Gunung Angsi)
K. pauciflora Hook. F	Melaka
K. profunda Markgr	Terengganu (Belara Forest Reserve)
K. terengganensis L. Allorge & Wiart	Terengganu (Dungun)
K. singapurensis Ridl.	Johor (Mersing)
K. sleeseniana Markgr.	Sarawak (Bintulu)
K. tenuis Leenh. & Steenis	Sarawak (Mattang)
K. teoi L. Allorge	Johor (Keluang)

The aim of this review is therefore to provide an overview of the chemical and pharmacological studies on indole alkaloids isolated from the *Kopsia* genera. For this mini-review, a comprehensive analysis and comparison of literature from various sources such as SciFinder®, Reaxys®, ScienceDirect®, PubMed Central®, NIH National Library of Medicine, Google Scholar and The Plant List® was conducted.

2. ALKALOIDS FROM *Kopsia* SPECIES

Plants belonging to this genus produce an abundance of indole alkaloids, many of which have an interesting carbon skeleton and biological activity (Kam, 1999). The first alkaloids from the genus *Kopsia* were determined in 1890 by Greshoff who worked on the seeds of *K. flavida* Blume, *K. arborea* Blume and *K. fruticosa* A. DC. Most species of the genus *Kopsia* comprises alkaloids derived from the aspidofractinine type which can be described as C_{18} linked to C_2. There was also the aspidospermane type which refers to an ethyl chain, and the eburnane type, which contains a linkage N_1-C_{16} (Sevenet et al., 1994). Figure 1 illustrates the structure of each type of alkaloid in the genus *Kopsia*. Researchers preferred the Mayer test, Dragendorff reagent or TLC followed by Dragendorff detection for the detection of alkaloids (Raal et al., 2020). Table 2 shows the *Kopsia* species whose alkaloid content has been reported.

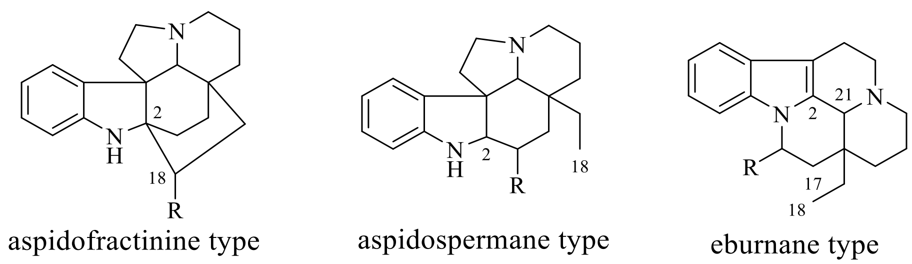

Figure 1. Indole alkaloid main skeleton isolated from *Kopsia* species

Table 2. *Kopsia* species and its reported alkaloids

Plant	Part	Isolated alkaloid	References
K. arborea	L	Methyl-12-methoxychanofruticosinate (**1**) Methyl-11,12-dimethoxychanofruticosinate (**2**) Methyl-N_1-decarbomethoxychanofruticosinate (**3**) Methyl-11,12-methylenedioxychanofruticosinate (**4**) Methyl-11,12-methylenedioxy-N_1-decarbomethoxychanofruticosinate (**5**) Methyl-11,12-methylenedioxy-N_1-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate (**6**) Arboricine (**7**) Arboricinine (**8**) Arborisidine (**9**) Arbornamine (**10**) Prunifoline A (**11**) Prunifoline B (**12**) Prunifoline C (**13**) Prunifoline D (**14**) Prunifoline E (**15**) Prunifoline F (**16**)	Lim et al., 2007 Lim & Kam et al., 2008 Wong et al., 2016 Wong et al., 2021
	SB	Arbolodinine A (**17**) Arbolodinine B (**18**) Arbolodinine C (**19**)	
K. dasyrachis	L	Kopsidasine (**20**) Kopsidasine-*N*-oxide (**21**) Kopsidasinine (**22**) Kopsirachine (**23**) Methyl-11,12-methylenedioxychanofruticosinate (**4**) Methyl-N_1-decarbomethoxychanofruticosinate (**3**) Methyl-11,12-methylenedioxy-N_1-decarbomethoxychanofruticosinate (**5**) 11,12-dimethoxykopsamine (**24**) Danuphylline (**25**) Kinabalurine G (**26**)	Kam et al., 1999a Kam et al., 1999c Saxton, 1998
	S	Kopsiflorine (**27**) Kopsilongine (**28**) 11-methoxykopsilongine (**24**) Kopsinine (**29**) Kopsinine-N_4-oxide (**30**) 11,12-methylenedioxykopsinaline (**31**) Tetrahydroalstonine (**32**) Pleiocarpamine (**33**) 16-hydroxymethylpleiocarpamine (**34**) Kopsine (**35**) *N*-carbomethoxy-5,22-dioxokopsane (**36**) (+)-eburnamonine (**37**) (+)-isoeburnamine (**38**) Leuconoxine (**39**) Paucidactine B (**40**) (−)-norpleiomutine (**41**) (−)-demethylnorpleiomutine (**42**) (+)-kopsoffinol (**43**) Kopsiflorine-N_4-oxide (**44**) Kopsilongine-N_4-oxide (**45**) Decarbomethoxykopsifine (**46**) Kopsinarine (**47**) 11,12-methylenedioxykopsine (**48**)	

		Dasyrachine (**49**)	
		Rhazinicine (**50**)	
		(+)-19(*R*)-hydroxyeburnamine (**51**)	
		(−)-19(*R*)-hydroxyisoeburnamine (**52**)	
	L, S	Kopsamine (**53**)	
		Kopsamine-N_4-oxide (**54**)	
		Pleiocarpine (**55**)	
		12-methoxypleiocarpine (**56**)	
		Kopsifine (**57**)	
K. deverrei	SB	(+)-kopsinone (**58**)	Mauger et al., 2021
		(−)-*N*-carbomethoxy-17*β*-hydroxykopsinine (**59**)	Saxton, 1998
		(−)-*N*-carbomethoxy-17*β*-hydroxy-$\Delta^{14,15}$-kopsinine (**60**)	
		(+)-*N*-methoxycarbonyl-12-methoxykopsinaline (**28**)	
		Kopsamine (**53**)	
		Pleiocarpamine (**33**)	
		16-hydroxymethylpleiocarpamine (**34**)	
	L	10-methoxykopsinone (**61**)	
		12-methoxykopsinone (**62**)	
		14,15-dihydro-10-methoxykopsinone (**63**)	
K. fruticosa	L, B	Kopsine (**35**)	Gilbert, 1965
	L	(−)-fruticosamine (**64**)	Teo et al., 1990
		(−)-fruticosine (**65**)	
K. griffithii	L	Kopsilongine (**28**)	Kam & Sim, 1998
		Kopsamine (**53**)	Kam et al., 1999b
		Kopsamine-N_4-oxide (**54**)	
		Pleiocarpine (**55**)	
		(+)-eburnamonine (**37**)	
		N-methoxycarbonyl-12-methoxy-Δ-^{16,17}-kopsinine (**66**)	
		N-carbomethoxy-11-hydroxy-12-methoxykopsinaline (**67**)	
		N-methoxycarbonyl-11,12-dimethoxykopsinaline (**24**)	
		Tetrahydroalstonine (**32**)	
		12-methoxykopsidasinine (**68**)	
		16-(*R*)-19,20-*E*-isositrikine (**69**)	
		12-methoxypleiocarpine (**56**)	
		Harmicine (**70**)	
	SB	(−)-eburnamine (**71**)	
		Kopsinine-N_4-oxide (**30**)	
		16-*epi*-deacetylakuammiline (**72**)	
		Rhazinaline N_4-oxide (**73**)	
		Akuammiline N_4-oxide (**74**)	
		16-*epi*-deacetylakuammiline-N_4-oxide (**75**)	
		11,12-methylenedioxykopsinaline-N_4-oxide (**54**)	
	L, SB	Harmane (**76**)	
		Leuconolam (**77**)	
		Leuconoxine (**36**)	
		Kopsinine (**29**)	
		Rhazimol (**78**)	
		Buchtienine (**79**)	
K. larutensis	L, B	(−)-eburnamonine (**37**)	Awang et al., 1991
		(−)-eburnamine (**71**)	Kam et al., 1992
		(+)-isoeburnamine (**38**)	Shahari et al., 2017
		(−)-kopsinine (**29**)	
		(−)-eburnaminol (**80**)	
		(+)-larutensine (**81**)	

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	S, B	(−)-kopsinine (**24**) Kopsilarutensinine (**82**) Tetrahydroalstonine (**32**)	
	L	(+)-eburnamonine (**37**) (+)-eburnamonine-N_4-oxide (**83**)	
K. macrophylla	L	Kopsilactone (**84**) Kopsone (**85**)	Kan-Fan et al., 1995 Sevenet et al., 1994
	B	5,22-dioxokopsane (**86**) Dregamine (**87**) Tabernaemontanine (**88**) Akuammiline (**89**) Rhazimol) (**78**) Norpleiomutin (**41**) Kopsoffine (**90**)	
	L, B	8-hydroxyskytanthine (**91**) 8-oxoskytanthine (**92**) 8-oxo-$\Delta^{5,9}$-skytanthine (**93**) 11,12-methylenedioxykopsinaline (**31**) 11,12-methylenedioxy 16-deoxykopsinaline (**94**)	
K. pauciflora	S	(−)-eburnamine (**71**) (+)-isoeburnamine (**38**) (+)-eburnamonine (**37**) (+)-eburnamenine (**95**) Norpleiomutine (**41**) *N*-methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**66**) Kopsamine-N_4-oxide (**24**) *N*-methoxycarbonyl-11,12-dimethoxykopsinaline (**24**) *N*-methoxycarbonyl-12-methoxykopsinaline (**28**) 12-methoxy-10-demethoxykopsidasinine (**68**) Larutienine B (**96**) 11,12-methylenedioxykopsinaline (**31**) (−)-19(*R*)-hydroxyisoeburnamine (**52**) (+)-19(*R*)-hydroxyeburnamine (**51**)	Gan et al., 2014; Kam & Yoganathan, 1996b; 1997
	L	Pauciflorine A (**97**) Pauciflorine B (**98**) Pauciflorine C (**99**) Paucifoline (**100**) Paucidactine A (**101**) Paucidactine B (**40**) Kopsirensine A (**102**) Kopsirensine B (**103**) Kopsirensine C (**104**) Catharinensine (**105**) Tetrahydroalstonine pseudoindoxyl (**106**) Andransinine A (**107**) Andransinine (**108**) Precondylcarpine (**109**) Larutensine (**81**) Arboloscine A (**110**) Leuconodine F (**111**) Mersicarpine (**112**) Leuconolam (**77**) Lahadinine A (**113**) Lahadinine B (**114**) Paucifinine (**115**) Paucifinine-*N*-oxide (**116**)	
	L, S	Larutienine A (**117**)	

		Leuconoxine (**39**) Rhazinilam (**118**) (+)-19(*R*)-hydroxyeburnamine (**51**) Tetrahydroalstonine (**32**) Kopsinine (**29**) *N*-methoxycarbonyl-11,12-methylenedioxykopsinaline (**53**) Kinabalurine A (**119**) Kinabalurine B (**120**) Kinabalurine C (**121**) Kinabalurine D (**122**) Kinabalurine E (**123**) Kinabalurine F (**124**) (+)-kopsoffine (**90**) (+)-kopsoffinol (**43**)	
K. profunda	S, L	(−)-N_1-methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine (**125**) (−)-N_1-methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$- kopsinine N_4-oxide (**126**) (−)-*N*-methoxycarbonyl-12-methoxy- $\Delta^{16,17}$-kopsinine (**66**) (−)-N_1-methoxycarbonyl-12-methoxy- $\Delta^{16,17}$-kopsinine N_4-oxide (**127**) (−)-N_1-methoxycarbonyl-12-hydroxy- $\Delta^{16,17}$-kopsinine (**128**)	Kam & Tan, 1995
K. terengganensis	B	(+)-quebrachamine (**129**) (−)-eburnamine (**71**) (+)-isoeburnamine (**38**) (−)-eburnaminol (**80**) (+)-larutensine (**81**) Terengganensines A (**130**) Terengganensines B (**131**)	Uzir et al., 1997
K. sleeseniana	L, B	Kopsingine (**132**)	Kam, 1999.
K. singapurensis	SB	11,12-methylenedioxykopsaporine (**133**) Singapurensine A (**134**) Singapurensine B (**135**) Singapurensine C (**136**) Singapurensine D (**137**) Aspidophylline A (**138**) Rhazinal (**139**) Kopsinine (**29**) 17*α*-hydroxy-$\Delta^{14,15}$-kopsinine (**140**) Kopsinganol (**141**) Rhazinilam (**118**) Leuconolam (**77**) Akuammidine (**142**) Tetrahydroalstonine (**32**)	Subramaniam et al., 2007
	L	Vincophylline (**143**) Kopsiloscine A (**144**) Kopsiloscine B (**145**) Kopsiloscine C (**146**) Kopsiloscine D (**147**) Kopsiloscine E (**148**) Kopsiloscine F (**149**) 16-*epi*kopsinine (**150**) Kopsilongine (**28**) Kopsilongine-*N*-oxide (**45**)	

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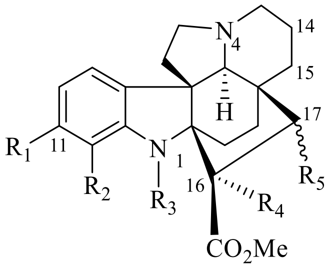
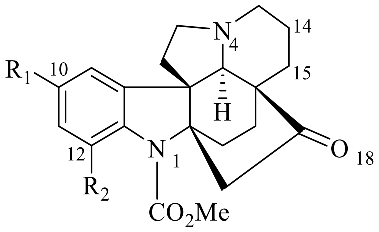
		Kopsidine D (**151**)	
	S, L	Kopsingine (**132**) 16-*epi*akuammiline (**152**) 16-*epi*deacetylakuammiline (**72**) Kopsaporine (**153**)	
K. tenuis	L	Lundurine A (**154**) Lundurine B (**155**) Lundurine C (**156**) Lundurine D (**157**) Tenuisine A (**158**) Tenuisine B (**159**) Tenuisine C (**160**) Tenuiphylline (**161**)	Kam et al., 2004
K. teoi	L, B	Kopsinol (**162**) Kopsinginol (**163**) Kopsinganol (**141**) Kopsingine (**132**) Kopsaporine (**153**) Rhazinilam (**118**) Rhazimol (**78**) Akuammiline (**89**) Kopsinginine (**164**) 17-α-hydroxy-$\Delta^{14,15}$-kopsinine (**140**)	Kam & Yoganathan, 1996a

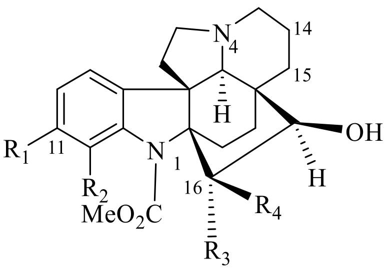
Aspidofractinine type



	R1	**R2**	**R3**	**R4**	**R5**
59	H	H	CO_2Me	H	OH
60	H	H	CO_2Me	H	OH, $\Delta^{14,15}$
31	OCH_2O		H	OH	H
140	H	H	H	H	α-OH, $\Delta^{14,15}$
29	H	H	H	H	H
30	H	H	H	H	H, N_4-O
94	OCH_2O		H	H	H
55	H	H	CO_2Me	H	H
56	H	OMe	CO_2Me	H	H

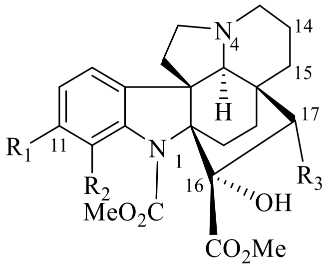


	R1	**R2**
58	H	H, $\Delta^{14,15}$
62	H	OMe
61	OMe	H, $\Delta^{14,15}$
63	OMe	H

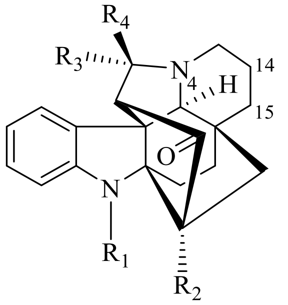


	R1	**R2**	**R3**	**R4**
162	H	H	CO_2Me	OH
163	H	H	H	H, $\Delta^{14,15}$
141	H	OMe	OH	CO_2Me, 15-α-OH

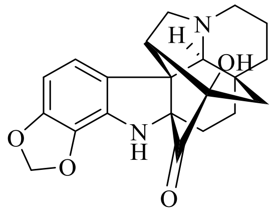
R1	**R2**	**R3**



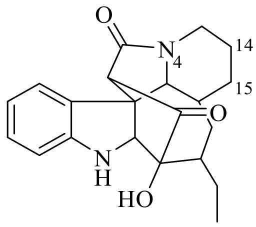
28	H	OMe	H
45	H	OMe	H, N_4-O
24	OMe	OMe	H
53	OCH_2O		H
54	OCH_2O		H, N_4-O
67	OH	OMe	H
153	H	OH	OH, $\Delta^{14,15}$
132	H	OMe	OH, $\Delta^{14,15}$
133	OCH_2O		OH, $\Delta^{14,15}$
27	H	H	H
44	H	H	H, N_4-O
164	H	CO_2Me	H, $\Delta^{14,15}$



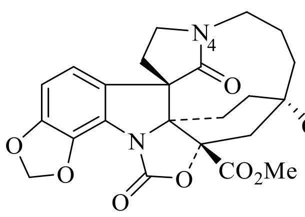
	R_1	**R_2**	**R_3**	**R_4**
35	CO_2Me	OH	H	H
86	H	H	O	
36	CO_2Me	H	O	



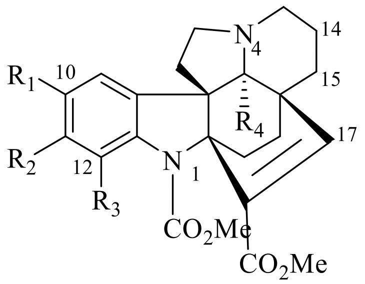
Dasyrachine (**49**)



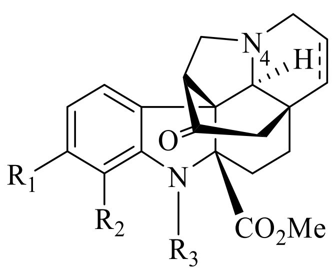
Kopsilarutensinine (**82**)



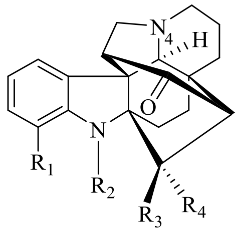
Paucifoline (**100**)



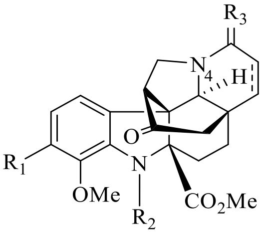
	R_1	**R_2**	**R_3**	**R_4**
20	OMe	H	H	OH
21	OMe	H	H	OH, N_4-O
125	H	OCH_2O		H
126	H	OCH_2O		H, N_4-O
66	H	H	OMe	H
127	H	H	OMe	H, N_4-O
128	H	H	OH	H



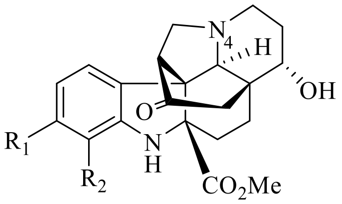
	R_1	**R_2**	**R_3**
5	OCH_2O		H
6	OCH_2O		H, $\Delta^{14,15}$
1	H	OMe	CO_2Me
2	OMe		CO_2Me
3	H	H	H
4	OCH_2O		CO_2Me



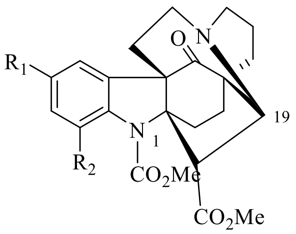
	R_1	R_2	R_3	R_4
65	H	CO_2Me	OH	H
64	H	CO_2Me	H	OH



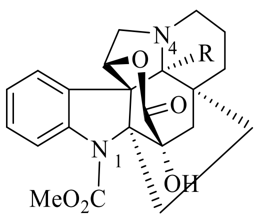
	R_1	R_2	R_3
11	H	CO_2Me	O
12	OMe	CO_2Me	H_2, $\Delta^{14,15}$
13	H	H	H_2, $\Delta^{14,15}$



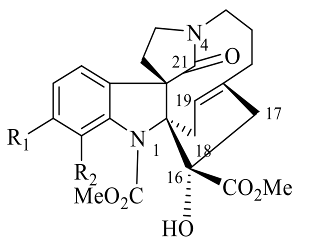
	R_1	R_2
14	H	H
15	OCH_2O	
16	H	OMe



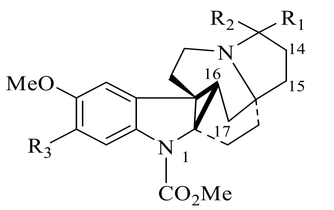
22 R_1=OMe, R_2=H
68 R_1=H, R_2=OMe



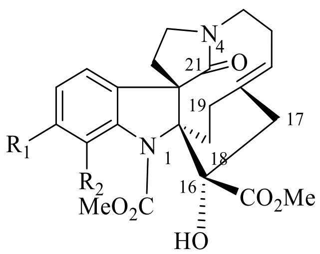
101 R=OH
40 R=H



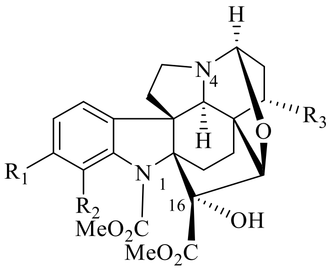
97 $R_1=R_2=OCH_2O$
98 $R_1=R_2$=OMe



154 R_1, R_2=O, R_3=H, $\Delta^{14,15}$
155 $R_1=R_2$=H, R_3=H, $\Delta^{14,15}$
156 $R_1=R_2=R_3$=H
157 $R_1=R_2$=H, R_3=OMe, $\Delta^{14,15}$



99 $R_1=R_2=OCH_2O$



134 $R_1=R_2$=H, R_3=OH
135 $R_1=R_2$=H, R_3=OMe
136 R_1, R_2= OCH_2O, R_3=OH,
137 R_1, R_2= OCH_2O, R_3=OMe
151 R_1=H, R_2=OMe, R_3= β-OH

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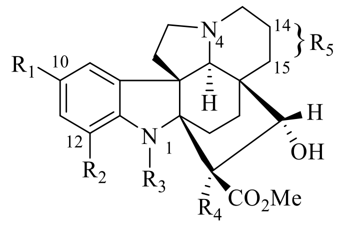
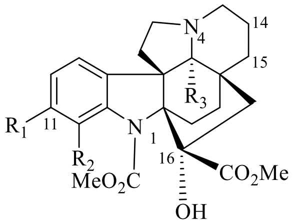
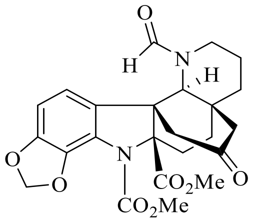


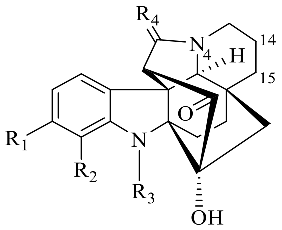
	R1	R2	R3	R4	R5
144	H	H	CO_2Me	OH	$\Delta^{14,15}$
145	H	H	CO_2Me	OH	NIL
146	H	H	CO_2Me	OH	15-α-OH
147	OMe	H	CO_2Me	OH	NIL
148	OMe	H	CO_2Me	OH	15-α-OH
149	H	OMe	CO_2Me	OH	15-α-OH



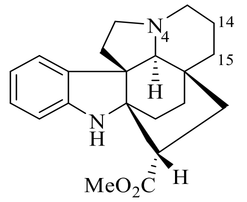
	R1	R2	R3
113	OCH_2O		CN
114	OMe	OMe	CN
115	OCH_2O		OH
116	OCH_2O		OH, N_4-O



Danuphylline (**25**)

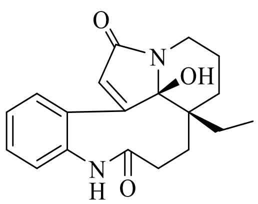


Kopsinarine (**47**)



16-epikopsinine (**150**)

Aspidospermane type



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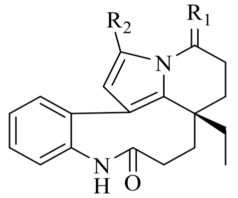
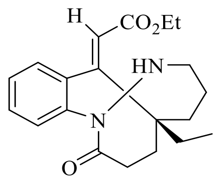
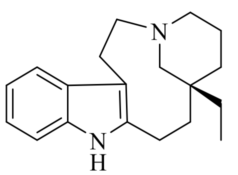


118 R_1= H_2, R_2=H
50 R_1= O, R_2=H
139 R_1= H_2, R_2=CHO



110



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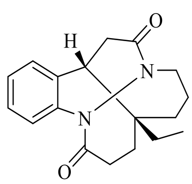

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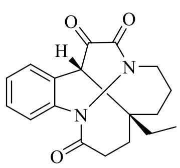
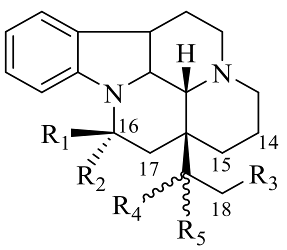


111

Eburnamine type



	R1	R2	R3	R4	R5
71	H	OH	H	H	H
38	OH	H	H	H	H
80	OH	H	OH	H	H
95	H		H	H	H, $\Delta^{14,15}$
37	O		H	H	H
83	O		H	H	H, N_4-O
51	H	OH	H	OH	H
52	OH	H	H	OH	H

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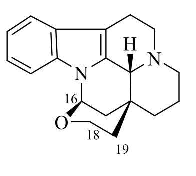
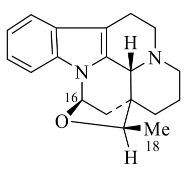
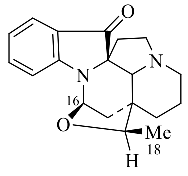
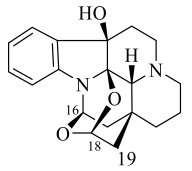
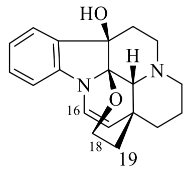

Larutensine (**81**)

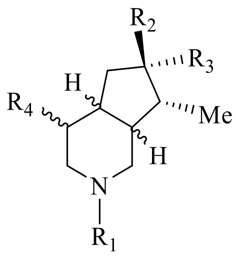

Larutienine A (**117**)


Larutienine B (**96**)

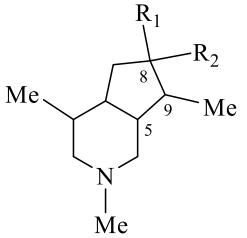

Terengganensine A (**130**)


Terengganensine B (**131**)

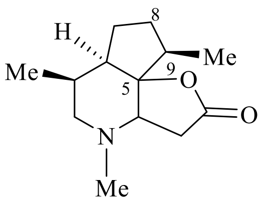
Piperidine type

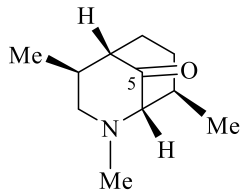


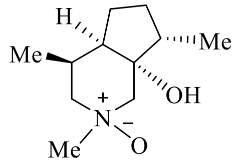
	R$_1$	**R$_2$**	**R$_3$**	**R$_4$**
119	Me	OH	H	*α*-Me, 5-*β*-H, 9-*α*-H
120	Me	O		*α*-Me, 5-*β*-H, 9-*α*-H
121	H	O		*α*-Me, 5-*β*-H, 9-*α*-H
122	Me	OH	H	*β*-Me, 5-*α*-H, 9-*β*-H
123	Me	O		*β*-Me, 5-*α*-H, 9-*β*-H
124	Me	OH	H	*β*-Me, 5-*α*-H, 9-*β*-H



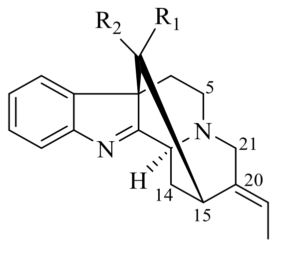
91 R$_1$=R$_2$=OH
92 R$_1$=R$_2$=O
93 R$_1$=R$_2$=O, $\Delta^{5,9}$


Kopsilactone (**84**)

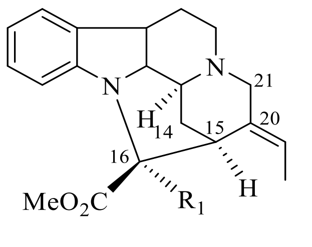

Kopsone (**85**)


Kinabalurine G (**26**)

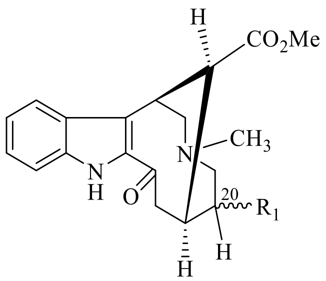
Corynane type



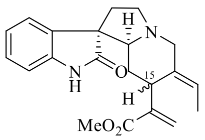
	R$_1$	**R$_2$**
78	CO_2Me	CH_2OH
72	CH_2OH	CO_2Me
75	CH_2OH	CO_2Me, N_4-O
89	CO_2Me	CH_2OAc
74	CO_2Me	CH_2OAc, N_4-O
152	CH_2OAc	CO_2Me



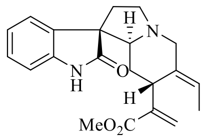
33 R$_1$=H
34 R$_1$=CH_2OH



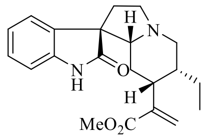
87 R$_1$=*α*-CH_2CH_3
88 R$_1$=*β*-CH_2CH_3



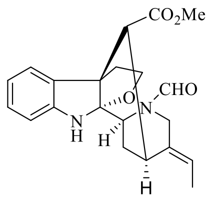
15α-H Kopsirensine A (**102**)
15β-H Kopsirensine B (**103**)



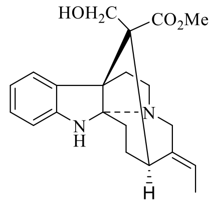
Kopsirensine C (**104**)



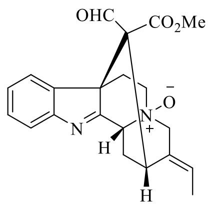
Catharinensine (**105**)



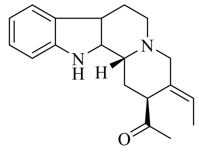
Aspidophylline A (**138**)



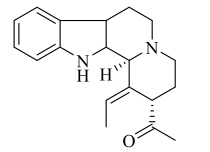
Vincophylline (**143**)



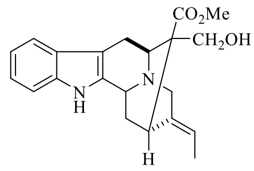
Rhazinaline N_4-oxide (**73**)



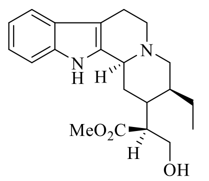
Arboricine (**7**)



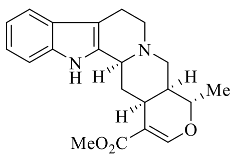
Arboricinine (**8**)



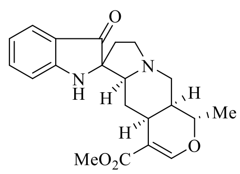
Akuammidine (**142**)



16-(*R*)-19,20-*E*-isositrikine (**69**)

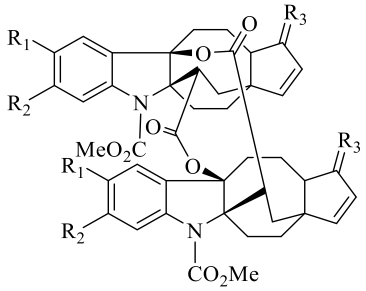


Tetrahydroalstonine (**32**)

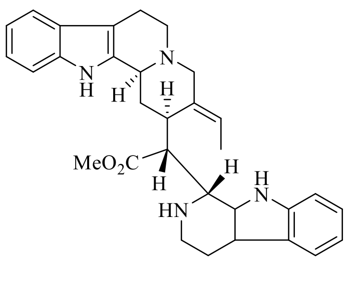


Tetrahydroalstonine pseudoindoxyl (**106**)

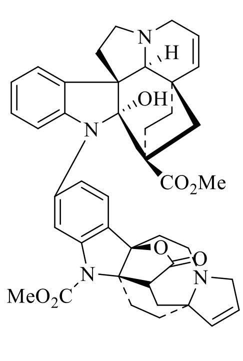
Bisindole type



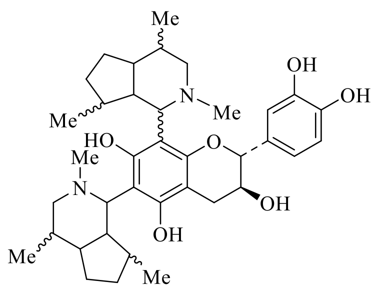
	R1	R2	R3
158	OMe	H	H_2
159	OMe	OMe	H_2
160	OMe	H	O



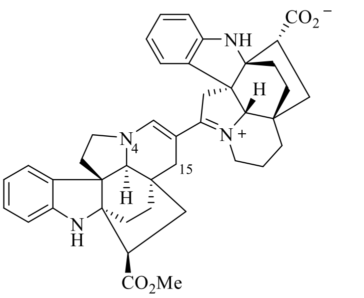
Buchtienine (**79**)



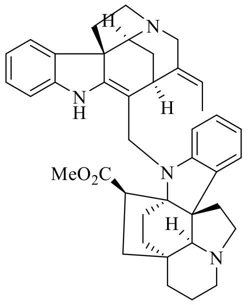
Tenuiphylline (**161**)



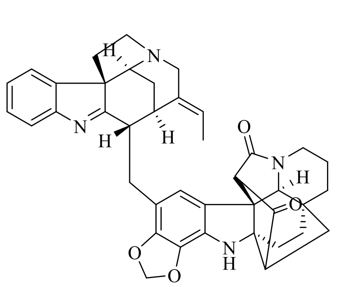
Kopsirachine (**23**)



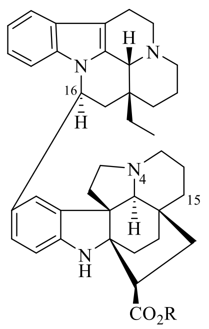
Arbolodinine A (**17**)



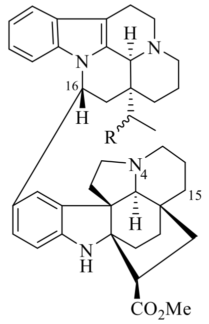
Arbolodinine B (**18**)



Arbolodinine C (**19**)

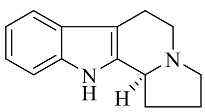


R= Me Norpleiomutine (**41**)
R= H Demethylnorpleimutine (**42**)

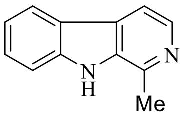


R=OH Kopsoffinol (**43**)
R=H Kopsoffine (**90**)

Harmane type

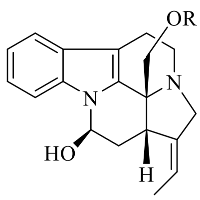


Harmicine (**70**)

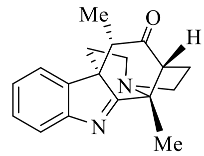


Harmane (**76**)

Abornane type

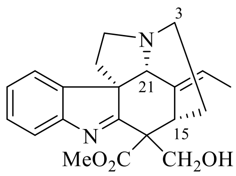


Arbornamine (**10**)

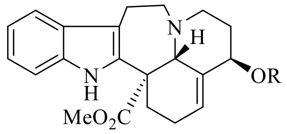


Arborisidine (**9**)

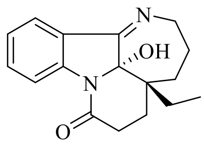
Uleine type



Precondylocarpine (**109**)



R=Me Andransinine A (**107**)
R=Et Andransinine (**108**)



Mersicarpine (**112**)

3. BIOLOGICAL ACTIVITIES FROM *Kopsia* SPECIES

Certain biological activity has been tested on the selected plant extract and their isolated alkaloids. Table 3 showed the compilation of the activities and the chemical constituents involved in the *Kopsia* species. To date, there have been no report on the biological activity of Malaysian species of *K. deverrei, K. profunda, K. sleeseniana* and *K. macrophylla*.

Table 3. *Kopsia* species and its reported biological activity

Species	Biological activity	Results	References

K. griffithi	Anti-leishmanial	In the preliminary test, **79, 33** and **76** showed positive results among all isolated alkaloids. **79** showed higher activity ($0.39<IC_{50}<1.56$ µg/mL) than **33** and **76** ($6.25<IC_{50}<25.00$ µg/mL) against *Leishmania donovani* (promastigote)	Kam & Sim, 1998
K. teoi	Anti-hypertensive	In anaesthetized spontaneously hypertensive rats (SHR), the use of compounds **132** and **153** resulted in linear dose-related decreases in the basal mean arterial blood pressure and concomitant fall in heart rate.	Mok et al., 1998
K. singapurensis	Anti-proliferative	Compounds **118** and **139** showed significant cytotoxicity toward drug-sensitive and against vincristine-resistant KB cells, a human oral epidermoid carcinoma cell line with IC_{50} of 0. 65 and 0.73 µM, respectively. Compounds **138**, **144**, **145**, and **147** showed potency in reversing drug resistance in drug-resistant KB cells with IC_{50} of 12.0, 3.8, 5.0, and 11.5 µM, respectively.	Subramaniam et al., 2007
K. tenuis	Anti-proliferative	Four compounds: **154, 155, 156** and **157** have been tested *in vitro* for their cytotoxicity towards B16 melanoma cells. Only **155** and **157** showed active potency with IC_{50} of 2.8 and 7.2 µg/mL.	Kam et al., 2004
K. pauciflora	Anti-proliferative	Compounds **97** and **98** are potent at the concentration of 13 and 25 µg/mL, respectively, in inhibitory activity against melanin biosynthesis in cultured B16 melanoma cells without any cytotoxicity towards the cells.	Kam et al., 1996c
		Compound **112** reversibly inhibited HL60, a human leukaemia cell line cycle progression in S-phase. This compound induced reactive oxygen species production and apoptosis at higher concentrations (above 30 µM).	Shiobara et al., 2021
K. dasyrachis	Anti-plasmodial	In the preliminary screening, the plant extract from DCM: MeOH (1:1) extraction showed a positive result (IC_{50} = 4.62 µg/mL) against the Gombak A strain of the malaria parasite, *Plasmodium falciparum*.	Khozirah et al., 2011
	Anti-proliferative	Compound **24** was found to have the ability to reverse multidrug resistance (MDR) in vincristine-resistant KB cells with the IC_{50} value of 1.6 µg/mL.	Kam et al., 1998
K. fruticosa	Anti-plasmodial activity	The DCM extract showed significant activity against the chloroquine-sensitive 3D7 strain of *P. falciparum* with EC_{50} of 7.14 µg/mL.	Wong et al., 2011
K. larutensis	Anti-allergic activity	Compounds **71**, **29**, **82** and **32** were tested for anti-allergic screening in the inhibition of *β*-hexosaminidase in RBL-2H3 cells. Compound **32** with IC_{10} of 11.78 µg/mL showed the highest percentage (61%) to inhibit the degranulation process of mast cells.	Shahari et al., 2017
K. arborea	Anti-proliferative	Compounds **17**, **18**, and **19** were tested for *in vitro* antiproliferative effects in various human cancer cell lines; KB, vincristine-resistant KB, PC-3, HCT116, HT-29, MDA-MB-231, MCF 7 and A549. Only compound **18** gives a pronounced inhibitory activity against those cells (IC_{50} ranging from 1.3-9.6 µM) whereas others were found ineffective (IC_{50}>10 µM).	Wong et al., 2021

K. terengganensis	Anti-proliferative	Different crude extracts of bark and leaves were subjected to toxicity test on KB cells. Results showed that the bark extract gives higher toxicity (ED_{50}=22µg/mL) compared to leaves (ED_{50}=60µg/mL).	Uzir et al., 1997

4. CONCLUSION

The phytochemical investigation of fourteen Malaysian *Kopsia* species resulted in the isolation of 164 indole alkaloids and most of them classified as aspidofractinine, aspidospermane, and eburnane types. Some species were found to possess medical properties and used to treat ailments such as anti-leishmanial, anti-hypertensive, anti-plasmodial, anti-allergic and anti-proliferative. However, it was still lacking in other *in vitro* and *in vivo* studies to prove the biological activities. Further research and clinical test can strengthen the properties of chemical constituents isolated in *Kopsia* species.

Declaration of Interest
The authors hereby declare that there is no conflict of interest.

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