CHEMICAL AND BIOACTIVE PRINCIPLES FROM SELECTED MALAYSIAN PLANTS

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***Résumé:** durant plusieurs années, un certain nombre de plantes ont été examinées dans le but de rechercher de nouvelles molécules et principes actifs. Des plantes sélectionnées dans les familles des Apocynacées, Euphorbiacées, Guttifères, Magnoliacées, Rubiacées et Rutacées ont fournis des produits naturels nouveaux et variés.*

***Abstract** : over the years a number of Malaysian plants have been examined for new chemical principles and some selected bioactivities. Selected plants from some families, e.g. Apocynaceae, Euphorbiaceae, Guttiferae, Magnoliaceae, Rubiaceae, and Rutaceae, have provided a variety of new and novel natural products.*

Introduction

The Malaysian flora is among the world's richest but their study has not been as rapid as the rapid development now taking place in the region. Over the last decade we have embarked on a program to study the phytochemistry and selected bioactivities of many of the available plant species and the results are summarised in this paper.

Biological Activities

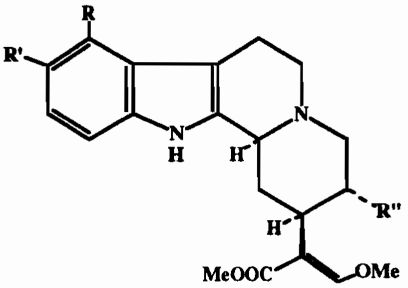
The screening of 32 Euphorbiaceae species and 3 Thymelaeaceae species for tumor promoter activity was carried out by means of a short-term in vitro assay using human lymphoblastoid cells latently infected with Epstein-Barr virus. All the Thymelaceae species and 11 of the Euphorbiaceae species were found to be positive for tumour promoter activity. Two of the plants, *Excoecaria agallocha* and *Wikstroemia ridley* were found to provide high activities.

The Euphorbiaceae family also provides the genus *Macaranga* of which the following species were screened for semiochemicals: *M. conifera, M. denticulata, M. diepenhorstii, M. gigantea, M. hypoleuca, M. heynei, M. hosei, M. hulletti, M. indica, M. javanica, M. lowii, M. perakensis, M. populifolia, M. quadricornis, M. recurvata, M. tanarius* and *M. triloba*. Several of the above species provide essential oils showing positive activities as semiochemicals.

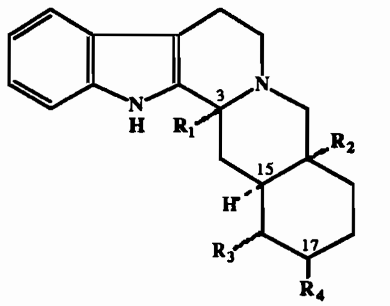
Several selected plants have been tested for antihypertensive activity on normotensive and spontaneously hypertensive rats. Among the plants which show promising results are *Andrographis panicalata, Averrhoa* species and several *Uncaria* species. *Portulaca oleraceae* provided hypertensive principles which include amine derivatives of phenylethane. Various alkaloids from *Uncaria* including dihydrocorynantheine (**1a**), gambirine (**1b**) and yohimbines were hypotensive.

Chemical Constituents

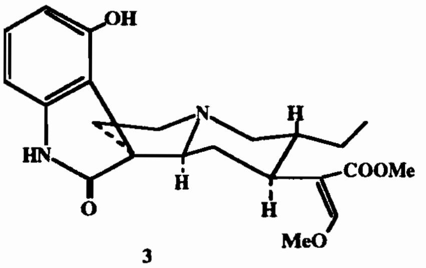
As expected a large number of natural products, many of them new or novel, were isolated from the plants studied. From *Uncaria* of the Rubiaceae family (*U. acida, U. borneensis, U. callophylla, U. elliptica, U. gambir, U. lanosa* and *U. longiflora*) a pattern of alkaloidal types may be discerned, namely the presence of tetra- and penta-cyclic heteroyohimbines and oxindoles. The results for *U. callophylla* are given below where it may be noted that novel dimeric indole alkaloids were isolated [1-4].



1a : R, R' = H, R" = Et
1b : R = OH, R' = H, R" = Et
1c : R = H, R' = OH, R" = Et
1d : R = OH, R' = H, R" = CH=CH$_2$



2a : R_1 = α-H; R_2 = β-H; R_3 = α-COOMe; R_4 = α-OH
2b : R_1 = α-H; R_2 = β-H; R_3 = α-COOMe; R_4 = β-OH
2c : R_1 = β-H; R_2 = β-H; R_3 = α-COOMe; R_4 = α-OH
2d : R_1 = α-H; R_2 = α-H; R_3 = β-COOMe; R_4 = α-OH
2e : R_1 = β-H; R_2 = β-H; R_3 = α-COOMe; R_4 = β-OH



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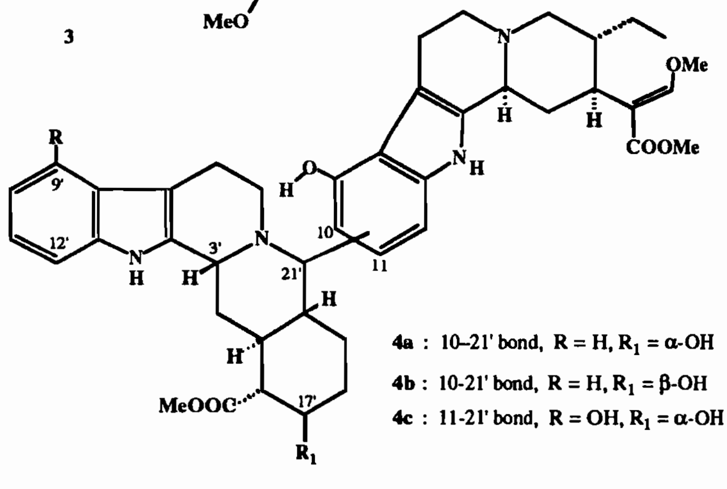
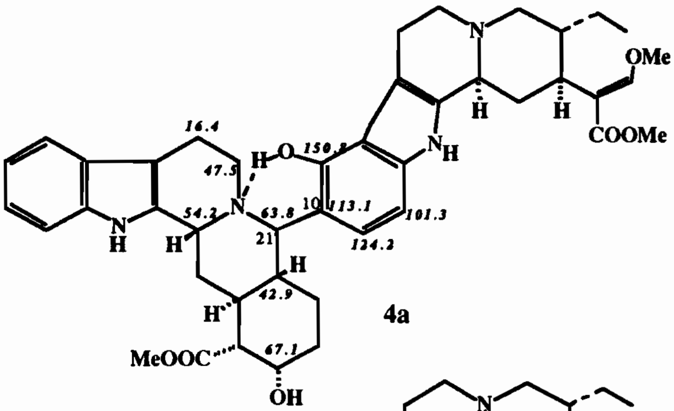
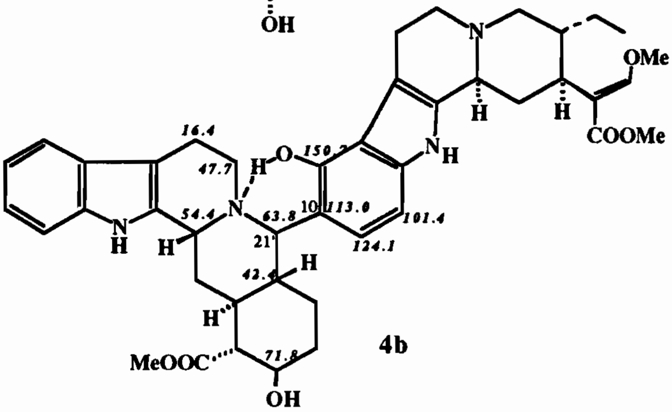


4a : 10-21' bond, R = H, R_1 = α-OH
4b : 10-21' bond, R = H, R_1 = β-OH
4c : 11-21' bond, R = OH, R_1 = α-OH

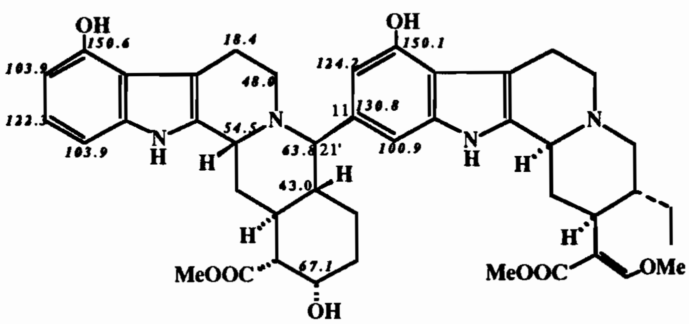
Apart from major compounds dihydrocorynantheine and gambirine (**1a,b**), isogambirine and gambireine (**1c, d**) are minor alkaloids. Although not all the yohimbines could be isolated from *U. callophylla* the ones listed could be found in this and other Uncaria studied. Although yohimbine isomers have been well studied, 3-epi-b-yohimbine (**2e**) has been isolated as a natural product for the first time [5]. Among the oxindoles rotundifoline (**3**) was isolated from while pteropodine and isopteropodine were found to be common in many *Uncaria* sp. studied. Noteworthy are dimeric indole alkaloids callophylline (**4a**), callophyline A (**4b**) and callophylline B (**4c**). **4a** was present in relatively larger amounts while dimeric indoles **4b,c** were minor alkaloids; all compounds were assigned on the basis of their 1D-NMR spectra. The formation of dimers are likely the result of an electrophylic attack of the corresponding iminium ions of monomeric alkaloids on the electron-rich alkaloid gambirine (**1b**) which is a major alkaloid. Characteristic CNMR shifts are instrumental to structure elucidation using only 1D-NMR techniques.



4a



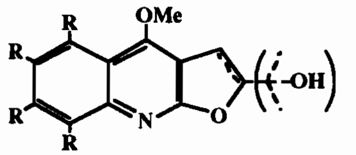
4b



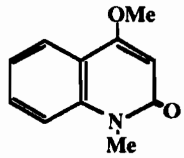
4c

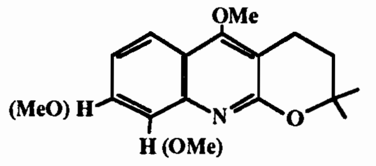
A number of Malaysian *Euodia* species including *E. enuera, E. latifolia, E. macrocarpa, E. pachyphylla, E. pilulifera* and *E. roxburghiana* have been investigated and various furoquinolines, pyranoquinolines and a quinolone were isolable as shown below. Additionally two monoterpenoid phloroacetophenone derivatives, melifoliones (**5**) were isolated. These have the structural feature of the quite rare desbenzylidenerubramin or bruceol [6] both of which were also elucidated by X-ray crystallography.

EUODIA Alkaloids

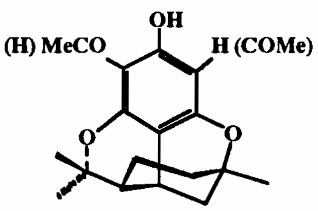


R = H, Me

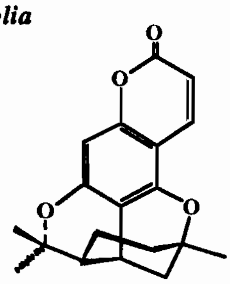




Euodia latifolia



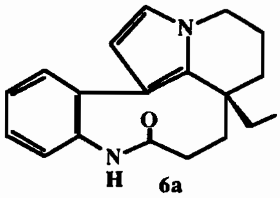
5 (mellifoliones)



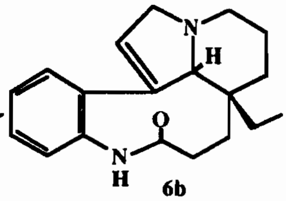
bruceol

Studies on plants of the genus *Kopsia* have provided a large number of alkaloidal types, of which rhazinilam (**6a**) from *K. singaporensis* is of interest because of its anti-tubulin activity. The same alkaloid is available together with dihydrorhazinilam (**6b**) and leuconolam (**6c**) from an earlier study on *Leuconotis griffithii* and *L. eugenifolia* [8-10]. *Kopsia* species (*K. profunda, K. larutensis* and *K. arborea*) have provided a rich harvest of alkaloidal types as illustrated below [11,12].

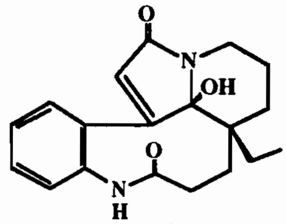
Leuconotis species



6a

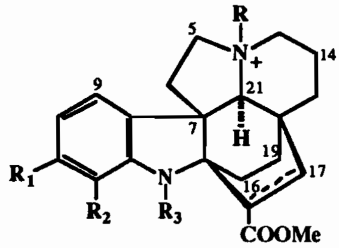


6b



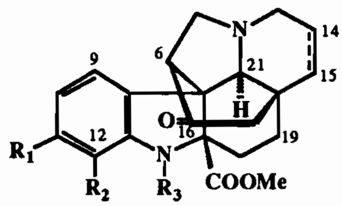
6c

Kopsia profunda



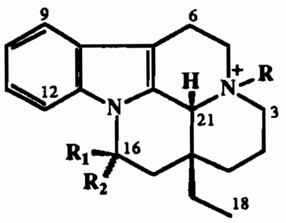
R_1 , R_2 = H, OMe, OH or OCH_2O
R_3 = H or COOMe
R = : or $-O^{\cdot}$

Kopsia arborea

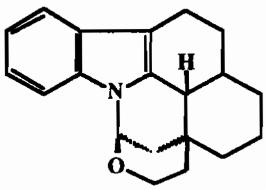


R_1 , R_2 = H or OCH_2O
R_3 = H or COOMe

Kopsia larutensis

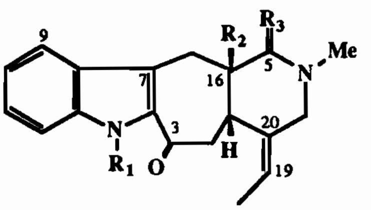


R_1 , R_2 = H, OH or =O
R = : or $-O^{\cdot}$



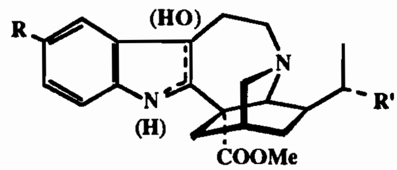
Tabernaemontana species are also widespread but they remain a taxonomically difficult group. Some of the varied alkaloid chemistry from *T. corymbosa* and *T. divaricata* are illustrated below [13].

Tabernaemontana corymbosa



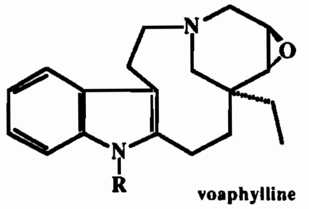
R_1 = H or OMe ; R_2 = H or CO_2Me
R_3 = H_2 or O

T. divaricata



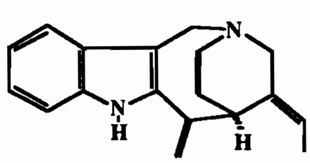
R = H or MeO ; R' = H or OH

T. divaricata



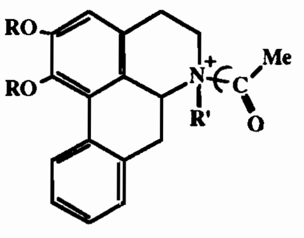
voaphylline

R = H or Me



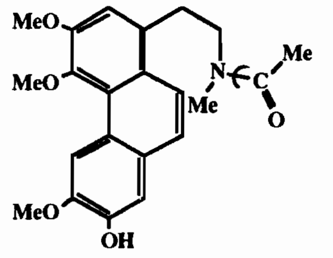
apparicine

Recent work on *Aromadendron elegans* (Magnoliaceae) has provided five known aporphine alkaloids and two new ones [14]. The structures of the new alkaloids **7** and **8** were elucidated by NMR techniques including COSY, HMBC, HMQC and NOESY experiments. Compounds **7a** and **8** are of interest since in the NMR spectra they can be seen to exist in E and Z forms which may be expected in view of the amide linkage.



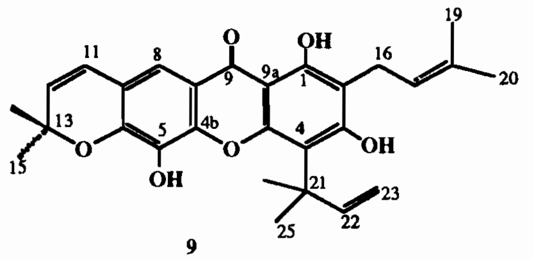
7a : R = Me, R' = :

7b : R,R = CH_2 , R' = O$^-$



8

The chemistry of the secondary metabolites of *Callophyllum inophyllum* and *Garcinia opaca* (Guttiferae) were also examined recently [14-16] and novel xanthones **9-11** were characterised by 2D-NMR techniques. These are given below. The HMBC technique is particularly useful in delineating ^2J and ^3J connectivities within the structural framework.



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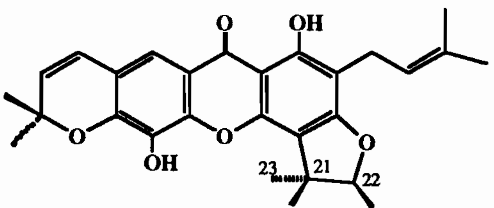

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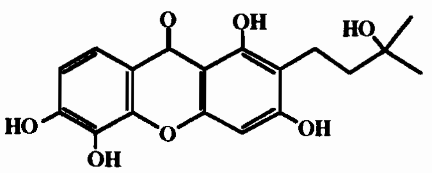

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References

1. Goh S.H. and Junan S.A., *Phytochem.* **24**, 880 (1985).
2. Goh S.H., Soepadmo E., Chang P., Aishah S., Koh Y.K, Nasrulhaq A., Taylor C.E. and Wong A.K., *Malaysian J. Sci.* **8**, 109 (1986).
3. Goh S.H., Lee K.H., Kam T.S. and Soepadmo E. In: Das, N.P. (ed.); *Flavonoids in Biology and Medicine III, Nat. Univ. Singapore* (1990), p. 139
4. Kam T.S., Lee K.H. and Goh S.H., *Phytochem.*, In Press (1991).
5. Lee K.H. *M.Sc. Thesis*, Univ. Malaya (1990).
6. Goh S.H., Chung V.C., Sha C.K. and Mak T.C.W., *Phytochem.* **29**, 1704 (1990).
7. Thoison O., Guenard D., Sevenet T., Kan-Fan C., Quirion J.C., Husson H.P., Chan K.C., Deverre J.R. and Potier P., *C. R. Acad. Sci.* Ser. II, **304**, 157.
8. Goh S.H., Chen Wei and Razak A., *Tetrahedron Lett.* **25**, 3483 (1984).
9. Goh S.H. and Razak A., *Tetrahedron Lett.* **27**, 2501 (1986).
10. Goh S.H., Razak A.and Wong W.H., *Tetrahedron* **24**, 7899 (1989).
11. Kam T.S. and Tan P.S., *Phytochem.* **29**, 2321 (1990).
12. Kam T.S., Tan P.S. and Hoong P.Y., In: *Proceedings of the Regional Conference on Medicinal Products from Tropical Rain Forests, Kuala Lumpur. May, 1991.*
13. Kam T.S., Loh K.Y., Loong W.L. and Lim L.H., In: *Proceedings of the Regional Conference on Medicinal Products from Tropical Rain Forests, Kuala Lumpur. May, 1991.*
14. Goh S.H. and Jantan I., Unpublished results.
15. Goh S.H., Jantan I., Gray A.I. and Waterman P.G., *Phytochem.*, In Press.
16. Goh S.H. and Jantan I., *Phytochem.* **30**, 366 (1991).

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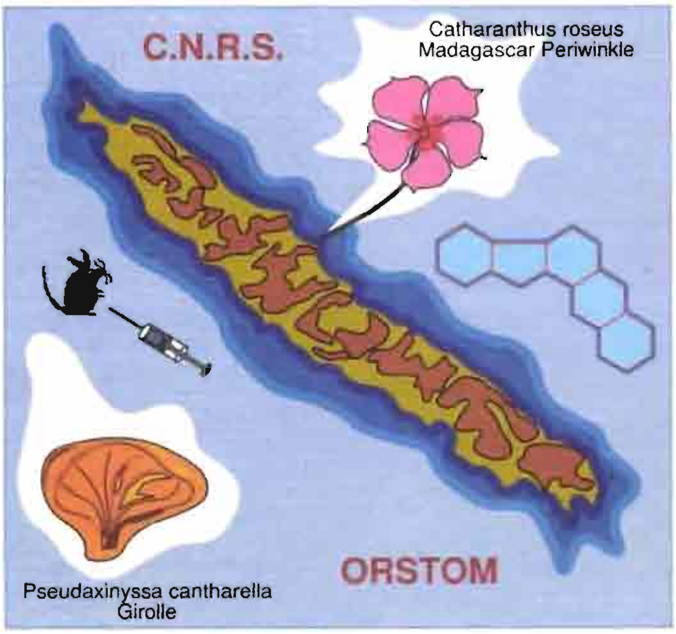

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