UNIVERSITY OF MALAYA
KUALA LUMPUR

DRUG DISCOVERY: THE SEARCH FOR THE 'MAGIC MOLECULES'

Professor Dr. Khalijah Awang
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Drug Discovery: The Search for the 'Magic Molecules'

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CURRICULUM VITAE

Name : Professor Dr. Khalijah Awang
Department : Chemistry
Faculty : Science
Field of Specialisation : Natural Products

No	Qualification	Class of Award	Year	Univ./ Institution
1	PhD (Natural Products)	Tres honorable (Very Honourable)	1993	Universite Rene Descartes, (University Paris V), France
2	MSc (Natural Products)		1990	University Malaya, Malaysia
3	BSc (Hons.) in Chemistry and minor in Environmental Studies	Honours	1987	University of Waterloo, Canada

ACADEMIC AWARDS:

No.	Name of Award / Prize	Awarding Body	Year of Award
1	Menier Prize (Best thesis in Pharmacognosy)	Universite Rene Descartes (Paris V)	1994
2	Anugerah Perkhidmatan Cemerlang	University Malaya	2002
3	Visiting Professor	JSPS	2005
4	Sijil Perkhidmatan Cemerlang 2007	University Malaya	2007

SUPERVISION

List of Students Supervised

Postgraduate	PhD	Master
Graduated	4	19
On-going	9	8

PhD (graduated)

No.	Name of candidate	Field of research / Title of thesis
1	Khalit Mohamad	Chemical constituents of Malaysian Meliaceae sp.
2	Ibtisam Abdul Wahab	Chemical constituents of Malaysian Dipterocarpaceae sp.
3	Mat Ropi Mukhtar	Chemical constituents of Malaysian Lauraceae sp
4	Yahia Fagiri	Physiological and biochemical studies on the Malaysian spirulina *(Arthrospira)* platensis and its potential as a feed supplement.

PhD (on-going)

No.	Name of candidate	Field of research / Title of thesis
1	Norsita Tohar	Bioassay-guided studies and standardization of water and CO_2 extract of *Mitragyna speciosa* for anti-inflammatory, analgesic and opioid dependent treatment
2	Kartini Ahmad	Alkaloids from *Neisosperma oppositifolia* and *Kopsia singapurensis* and development of synthetic methodology of indole alkaloids
3	Wan Lelly Heffen	Bioassay guided studies of selected Curcuma sp.
4	Ahmad Kaleem	Chemical constituents of Neolamarckia sp.
5	Omar Hamdi	Bioassay guided studies of selected Curcuma sp.
6	Saraswaty a/p Vellu	Synhesis of phenolics from stilbenes
7	Mahdi Faravani	Allelopathy plants: Melastoma malabathricum

No.	Name of candidate	Field of research / Title of thesis
8	Tiah Rachmatiah	Chemical constituents from selected Lauraceae sp.
9	Norhayati Abdullah	Bioassay guided study of selected Malaysian medicinal plant.

MSc (graduated)

No.	Name of candidate	Field of research / Title of thesis
1	Khalit Mohamad	Chemical constituents of Malaysian Meliaceae sp.
2	Rozana Othman	Chemical constituents of *Kaempheria galanga*
3	Mazdida	Chemical constituents of *Fissistigma sp.*
4	Shasya Uzir	Chemical constituents of *Kopsia trengganensis*
5	Norsita Tohar	Essential oils of *Plumeria sp.*
6	Mardiana Saaid	Chemical constituents of selected Annonaceae sp.
7	Zunoliza Abdullah	Chemical constituents of selected Annonaceae sp.
8	Satariah Hassan	Chemical constituents of selected Piperaceae sp.
9	Norhayati Abdullah	Chemical constituents of *Andrographis paniculata*
10	Saraswati a/p Vellu	Chemical constituents of *Hunteria zeylanica*
11	Ahmad Nazif Aziz	Chemical constituents and biological activities of *Alpinia conchigera*
12	Mohd Fadzli Md Din	Alkaloids of *Cyathostemma wrayi* King
13	Vicky Bihud	Alkaloids of *Artabotrys pleurocarpus*
14	Abd. Rashid Li	Phytochemical studies on *Meiogyne virgata* (Registered at UiTM)
15	Rosliza Ali	Alkaloids from *Phoebe grandis*
16	Tengku Farah Wahida Ku Chik	Chemical Constituents of *Goniothalamus fulvus*
17	Adlin bt. Afzan Abdul Wahab	Chemical Constituents of the bark of *Goniothalamus giganteus*

Master (on-going)

No.	Name of candidate	Field of research / Title of thesis
1	Devi Rosmy Syamsir	Essential Oils and Biological Activities of three wild *Alpinia* sp.
2	Chan Gomathi	Bioasssay-guided Isolation of Acetyl Cholinesterase Inhibitory Components from *Mesua elegans* (King) Kosterm
3	Fadzly Azhar Kamaruzaman	Chemical Constituents of Meliaceae sp.
4	NoorAimi Othman @ Ghazali	Alkaloids of *Kopsia singapurensis*
5	Mahfuzah Yusoff	Chemical Constituents of Meliaceae sp.
6	Mohamad. Nurul Azmi Mohamad. Taib	Isolation of 1'-acetoxychavicol acetate, synthesis of its analogue and biological activities of *Alpinia conchigera*
7	Mehran	Chemical Constituents of *Ochrosia oppositifolia*
8	Norhafiza Saidan	Phytochemicals and Biological Activity of Malaysian *Morinda citrifolia* (Registered at UiTM)

PUBLICATIONS

(1) Chapter or Part of Academic Books/ Text Books / Encyclopedias

1. Khalijah Awang, Halijah Ibrahim, C.W. Khoo, Faridahanim Jaafar, Mat Ropi Mukhtar, Teo Leong Eng, A. Hamid A. Hadi and Noorain Abdullah, Antiplasmodial alkaloidal plant extracts from the Endau-Rompin forest, Johor Malaysia. *In The Forest and Biodiversity of Selai, Endau-Rompin*. Universiti Malaya, Kuala Lumpur, 2007, 121-128.

2. Khalijah Awang, Mat Ropi Mukhtar and A.Hamid A. Hadi, "The Proaporphine – Tryptamine Dimers", J.N. Govil et al.(Eds) Recent Progress in Medicinal Plants *(Phytochemistry and Pharmacology III)*, 2007, 17, 21-36.

3. Khalijah Awang, *"Ensiklopedia Sains dan Teknologi"*, Dewan Bahasa dan Pustaka/UTM, Linus Pauling, 2007, 305-306.

4. Khalijah Awang, *"Ensiklopedia Sains dan Teknologi"*, Dewan Bahasa dan Pustaka / UTM, Alkaloid, 2007, 15-18.

5. Faridahanim, M.J., Abdul Hamid, A.H., Khalijah A., Nor Hadiani, I., Noor Rain, A., " The Screening of the Extract from *Leuconotis eugenifolius* for Antimalarial Activity using Lactate Dehydrogenase Assay, Fasihuddin b. Ahmad et al.(Eds), UNIMAS, 2006, 23-26.

6. Chong, S.L., Khalijah, A., Khalit, M, "Chemical Constituents of *Chisocheton erythrocarpus"* Fasihuddin b. Ahmad et al.(Eds), UNIMAS, 2006, 187-190.

7. Saripah Salbiah S.A.A., Abdul Hamid, A.H., Khalijah, A., Mat Ropi, M., "Alkaloids from *Artabotrys suaveolens*", Fasihuddin b. Ahmad *et al.*(Eds), UNIMAS, 2006, 301-304.

8. Saripah Salbiah S.A.A., Abdul Hamid, A.H., Khalijah, A., Mat Ropi, M., "Alkaloids from *Popowia perakensis*", Fasihuddin b. Ahmad *et al.* (Eds), UNIMAS, 2006, 311-314.

(2) List of selected Journal Publications

1. H. Ibrahim, A.N. Aziz, D.R. Syamsir, N.A. Mohamad Ali, M. Mastura., R. Mat Ali and K. Awang, (2009), Essential oils and Bioactivities of *Alpinia conchigera* Griff., Food Chemistry, 113(2), 575-577.

2. Faravani M., H. B. Baki and A. Khalijah, (2008), Assessment of Allelopathic Potential of *Melastoma malabathricum L.* on *Radish raphanus sativus* L. and Barnyard Grass *(Echinochloacrus-galli)*. Journal of Notulae Botanicae Horti Agrobotanici Cluj-Napoca, 36 (2), 54-60.

3. Alessandra Maia, Isabelle Schmitz-Afonzo, Marie-Therese Martin, Khalijah Awang, Oliver Laprevote, Francoise Gueritte and Marc Litaudon, (2008), Acylphenols from *Myristica crassa* as New Acetylcholinesterase Inhibitors, Planta Medica, 74(12), 1457-1462.

4. Khalijah Awang, Kartini Ahmad, Noel F. Thomas, Yusuke Hirasawa, Koichi Takeya, Mat Ropi Mukhtar, Khalit Mohamad, Hiroshi Morita, (2008), Singaporentine A, a new indole alkaloid from *K. singapurensis,* Heterocycles, 75 (12).

5. Khalit Mohamad, Yusuke Hirasawa, Chong Soon Lim, Khalijah Awang, A. Hamid A. Hadi, Koichi Takeya and Hiroshi Morita, (2008), Ceramicine A and walsogyne A, novel limonoids from two species of Meliaceae, Tetrahedron Letters. 49(27), 4276-4278.

6. Chin Hui Kee, Noel F. Thomas, Azhar Ariffin, Khalijah Awang and Seik Weng Ng, (2008), (E)-N-[2-(Biphenyl-4-ylvinyl)phenyl]furan-2-carboxamide, Acta Crystallographica Section E, E64, 2210.

7. Nor Hadiani Ismail, Che Puteh Osman, Khalijah Awang, Sri Nurestri Abdul Malek and Seik Weng Ng, (2008), 2-Formyl-3-hydroxy-9,10-anthroquinone, Acta Crystallographica Section E, E64, 2164

8. Ibrahim A. Najmuldeen, Abdul Hamid Abdul Hadi, Khalijah Awang, Khalit Mohamad and Seik Weng Ng, (2008), 17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]-phenanthrene-3,7-diol from *Chisocheton tomentosus* (Meliaceae), Acta Crystallographica Section E, E64, 2163.

9. Gomathi Chan, Khalijah Awang, A. Hamid A. Hadi and Seik Weng Ng, (2008), 6-[(E)-3,7-Dimethylocta-2,6-dienyl]-5,7-dihydroxy-8-(2-methylbutanoyl)-4-phenyl-2*H* chromen-2-one from *Mesua kunstleri* King (Kosterm), Acta Crystallographica Section E, E64, 1332.

10. Mat Ropi Mukhtar, Mohd Azlan Nafiah, Khalijah Awang, A.Hamid A.Hadi and Seik Weng Ng, (2008), 2, 7-Dihydroxy-3, 6-dimethoxy-phenanthrene from *Dehaasia longipedicellata*, Acta Crystallographica Section E, E64, 1135.

11. Khalijah Awang, Nor Hadiani Ismail, Rohaya Ahmad, Nor Hafizoh Saidan and Pascal Retailleau, (2008), 1, 3-Dihydroxy-9, 10-dioxo-9, 10-dihydroanthracene-2-carbaldehyde, Acta Crystallographica Section E, E64, 597.

12. Noel Francis Thomas, Chin-Hui Kee, Azhar Ariffin, Khalijah Awang, Jean-Frederic Faizal Weber, Chuan-Gee Lim, Mat Ropi Mukhtar and A. Hamid A. Hadi, (2008), The Subtle Co-Catalytic Intervention of Benzophenone in Radical Cation Mediated Cyclization- An Improved Synthesis of 2-(3', 4'-Dimethoxyphenyl) Indole, Heterocycles, 25(5), 1097-1108.

13. Khalijah Awang, A. Hamid A. Hadi, Nurdin Saidi, Mat Ropi Mukhtar, Hiroshi Morita, Marc Litaudon (2008), New phenantrene alkaloid isolated from *Cryptocarya crassinervia* Miq., Fitoterapia, 79(4), 308-310.

14. Mat Ropi Mukhtar, A.Hamid A.Hadi, David Rondeau, Pascal Richomme, Marc Litaudon, M.Rais Mustafa and Khalijah Awang (2008), New proaporphines from the bark of *Phoebe scortechinii*, Natural Product Research, 22(11), 921-926.

15. K. Awang, M.R. Mukhtar, A.H.A. Hadi, (2007), The proaporphine-tryptamine dimers, Recent progress in Medicinal Plants, 17, 21-36.

16. Khalit Mohamad, Tomoko Suzuki, Yuki Baba, Kazumasa Zaima, Yosuke Matsuno, Yusuke Hirasawa, Mat Ropi Mukhtar, Khalijah Awang, A.Hamid A. Hadi and Hiroshi Morita, (2007), Huncaniterine A, A new Bisindole Alkaloid from *Hunteria zeylanica*, Heterocycles, 74, 969-976.

17. Khalijah Awang, Mat Ropi Mukhtar, M. Rais Mustafa, Marc Litaudon, Khozirah Shaari, Khalit Mohamad and A. Hamid A. Hadi, (2007), New Alkaloids from *Phoebe scortechinii*, Natural Product Research, 21(8), 704-709.

18. N. Saidi, M.R. Mukhtar, K. Awang, A. H. A. Hadi and S. W. Ng. (2007), 6,7,8-Trimethoxycoumarin from *Cryptocarya bracteolate*, Acta Crystallographica Section E, E63, 3692-3693.

19. Khalijah Awang, Saripah Salbiah Syed Abd. Azziz, A. Hamid A. Hadi, Hiroshi Morita, Yusuke Hirasawa, Toru Lizuka, Marc Litaudon and Mat Ropi Mukhtar, (2007), Pecrassipines A and B, Seco-bisgenzylisoquinoline alkaloids from *Phaenthus crassipetalus*, Heterocycles, 71(9), 2055-2061.

20. Khalijah Awang, Chong Soon Lim, Khalit Mohamad, Hiroshi Morita, Yusuke Hirasawa, Koichi Takeya, Odile Thoison and A. Hamid A. Hadi, (2007), Erythrocarpines A-E, new cytotoxic limonoids from *Chisocheton erythrocarpus*, Bioorganic & Medicinal Chemistry, 15(17) 5997-6002.

21. R. Othman, M.R. Mustapha, M. Ali Mohd., H. Ibrahim, K. Awang, (2006), Bioassay guided isolation of a vasorelaxant active compound from *Kaempferia galanga* L., Phytomedicine, 13(1-2), 61-66.

22. Khalijah Awang, Mat Ropi Mukhtar, A. Hamid A. Hadi, Marc Litaudon, Jalifah Latip, Noor Rain Abdullah, (2006), New alkaloids from *Phoebe grandis* (Nees) Merr., Natural Product Research, 20(6), 567-572.

23. Norsita Tohar, Mustafa A. Mohd., Ibrahim Jantan and Khalijah Awang, (2006), A comparative study of the essential oils of the genus *Plumeria* Linn. from Malaysia" Flavour and Fragrance Journal, 21(6), 859-863.

24. Norsita Tohar, Mustafa A. Mohd., Ibrahim Jantan and Khalijah Awang, (2006), Chemical Composition of the Essential Oils of Four *Plumeria* Species Grown on Peninsular Malaysia, Journal of Essential Oil Research, 18(6), 613-617.

25. Hiroshi Morita, Khalijah Awang, A. Hamid A. Hadi, Koichi Takeya, Hideji Itokawa, Jun'ichi Kobayashi, (2005), Conformational analysis of rhazinilam and three dimensional quantitative structure-activity relationships of rhazinilam analogues, Bioorganic and Medicinal Chemistry Letters, 15(4), 1045-1050.

26. Khalijah Awang, Hiroshi Morita, Mat Ropi Mukhtar, Khalit Mohamad, A. Hamid A. Hadi, (2005), Malayan Flora: The Natural Producer of Lead Compounds, Yakugaku Zasshi, 125(3), 270-273.

27. Ibrahim Noorbatcha, Khalit Mohamad, O.R. Omobuwajo, Khalijah Awang, (2005), "Computer Modeling Studies of Apotirucallane Triterpenes in solution", Malaysian Journal of Science, 24(2), 17-123.

28. Khalijah Awang, Faridahanim Mhd. Jaafar, A. Hamid A. Hadi, (2005), Indole alkaloids of *Leuconotis eugenifolius*, Malaysian Journal of Science, 24, 129-132.

29. Khalijah Awang, Zunoliza Abdullah, (2005), Chemical Constituents of *Desmosdunalii*, Malaysian Journal of Science, 24, 267-271.

30. M.R. Mukhtar, A. Hamid A. Hadi, M. Litaudon, K. Mohamad, K. Awang, (2005), New Bisbenzylisoquinoline (BBIQ) alkaloids from *Dehaasia immerate* (Jack) Kosterm, Malaysian Journal of Science, 24, 69-74.

31. K. Awang, M. Saaid, (2005), Alkaloids of *Fissistigma manubriatum*, Malaysian Journal of Science, 24, 41-46.

32. K. Awang, M. Saaid, (2005), Alkaloids of *Polyalthia sclerophylla*, Malaysian Journal of Science, 24, 47-50.

33. Noel F. Thomas, Saraswati S. Velu, J. F. Weber, Ibrahim Noorbatcha, A. Hamid A. Hadi, Khalijah Awang, (2004), A tandem highly stereoselective $FeCl_3$ – promoted synthesis as a bisindoline; synthetic utility of radical cations in heterocyclic construction, Tetrahedron, 60(51), 11733-11742.

34. Mat Ropi Mukhtar, A. Hamid A. Hadi, Thierry Sevenet. Marie-Therese Martin and Khalijah Awang, (2004), Phoebegrandine C, a novel proaporphine-tryptamine dimer, from *Phoebe grandis* (Nees) Merr., Natural Product Research, 18(2), 163-167.

35. Mat Ropi Mukhtar, A. Hamid A. Hadi, M. Litaudon, Khalijah Awang, (2004), Morphinandienone alkaloids from *Dehaasia longipedicellata*, Fitoterapia, 75(7-8), 792-794.

36. Mazdida Sulaiman, A. Hamid A. Hadi, Khalijah Awang, (2003), Alkaloids and flavones from *Desmos dumosus* Roxb., Malaysian Journal of Science, 22(1), 87-93.

37. N. F. Thomas, K. C. Lee, T. Paraidathathu, J-F. Weber, K. Awang, D. Rondeau, P. Richomme, (2002), Tandem pericyclic reactions in a new $FeCl_3$-promoted synthesis of catechol analogues of restrytisol, Tetrahedron, 58(36), 7201-7206.

38. R. Othman, H. Ibrahim. M. A. Mohd, K. Awang, A. H. Gilani, M. R. Mustafa, (2002), Vasorelaxant effects of thyl cinnamate isolated from *Kampferia immer* a on smooth muscles of the rat aorta, Planta Medica, 68(7), 655-657.

39. N. F. Thomas, K. C. Lee, T. Paraidathathu, J. F. F. Weber, K. Awang, (2002), Manganese triacetate oxidative lactonisation of electron rich stilbenes possessing catechol and resorcinol substitution, Tetrahedron Letters, 43(17), 3151-3155.

40. Mat Ropi Mukhtar, A. Hamid A. Hadi, Khalijah Awang, (2003), Proaporphine-tryptamine dmer- a review, Jurnal Sains, 11(1), 1-8.

41. K. Awang, A. Hamid A. Hadi, (2000), Alkaloids from *Fissistigma fulgens* Merr. (Annonaceae), Malaysian Journal of Science, 19, 41-44.

42. C. Wiart, M-T. Martin, K. Awang, N. Hue, L. Serani, O. Laprevote, M. Pais, M. Rahmani, (2001), Sesquiterpenes and alkaloids from *Scorodocarpus borneensis*, Phytochemistry, 58(4), 653-656.

43. J-F. Weber, I. A. Wahab, A. Marzuki, A. A Kadir, N. F. Thomas, A. Hamid a. Hadi, K. Awang, A. A. Latif, P. Richomme, J. Delaunay, (2001), Heimiol A, a new dimeric stilbenoid from *Neobalanocarpus heimii*, Tetrahedron Letters, 42(29), 4895-4897.

44. M. R. Mukhtar, K. Awang, A. Hamid A. Hadi, (2000), Chemical Constituents and Bioactive Compounds of *Goniothalamus tortilipetalus* Hend. (Annonaceae), Malaysian Journal of Science, 19, 7-12.

45. M. R. Mukhtar, K. Awang, A. Hamid A. Hadi, (2000), Chemical constituents of *Phoebe grandis* (Nees) Merr. (Lauraceae), Malaysian Journal of Science, 19, 67-70.

46. R. Othman, M. Sulaiman, S. Uzir, K. Awang, A. Hamid A. Hadi, (1999), Chemical constituents of three Malaysian Annonaceae, Malaysian Journal of Science, 18, 35-40.

47. N. A. Wahab, Y. Ashril, K. Awang, A. Hamid A. Hadi, (1999), Testing of *Kaempferia immer* a extracts against cancer cell lines, Malaysian Journal of Science, 18, 31-33.

48. N. A. Wahab, Y. Ashril, K. Awang, A. Hamid A. Hadi, (1999), Protocol for screening cytotoxic activity of natural products against KB cells, Malaysian Journal of Science, 18, 27-29.

49. K. Mohamad, M-T. Martin, H. Nadjar, C. Gaspard, T. Sevenet, A. Hamid A. Hadi, K. Awang, M. Pais, (1999), Cytotoxic 3,4-secoapotirucallanes from *Aglaia argentea* bark, Journal of Natural Products, 62(6), 868-872.

50. K. Mohamad, T. Sevenet, V. Dumontet, M. Pais, A. Hamid A. Hadi, K. Awang, M-T. Martin, (1999), Dammarane triterpenes and pregnane steroids from *Aglaia lawii* and *A. tomentosa*, Phytochemistry, 51(8), 1031-1037.

51. M. Sulaiman, M-Y. Martin, M. Pais, A. Hamid A. Hadi, K. Awang, (1998), Desmosine, an artifact alkaloid from *Desmos dumosus*, Phytochemistry, 49(7), 2191-2192.

52. K. Mohamad, M-T. Martin, E. Leroy, C. Tempete, T. Sevenet, K. Awang, M. Pais, (1997), Argenteanones C-E and Argenteanols B-E, Cytotoxic Cycloartanes from *Aglaia argentea*, J. Nat. Prod., 60(2), 81-85.

53. S. Uzir, A. M. Mustapha, A. Hamid A. Hadi, K. Awang, C. Wiart, J-F. Gallard, M. Pais, (1997), Terengganensis A and B dihydroeburnane alkaloids from *Kopsia terengganensis*, Tetrahedron Letters, 38(9), 1571-1574.

54. M. Ropi Mukhtar, M-T. Martin, M. Domansky, M. Pais, A. Hamid A. Hadi, K. Awang, (1997), Phoebegrandines A and B, proaporphines-tryptamine dimers from *Phoebe grandis*, Phytochemistry, 45(7), 1543-1546.

55. B. David, T. Sevenet, O. Thoison, K. Awang, M. Pais, M. Wright, D. Guenard, (1997), Hemisynthesis of Rhazinilam analogues: structure-activity relationship on tubulin-microtubule system, Bioorganic and Medicinal Chemistry Letters, 7(17), 2155-2158.

56. O.R. Omobuwajo, M-T. Martin, G. Perromat, T. Sevenet, K. Awang, M. Pais, (1996), Cytotoxic cycloartanes from *Aglaia argentea*, Phytochemistry, 41(5), 1325-1328.

57. O.R. Omobuwajo, M-T. Martin, G. Perromat, T. Sevenet, M. Pais, K. Awang, (1996), Apotirucallane triterpenes from *Aglaia argentea* , J. Nat. Prod., 59(6), 614-617.

58. Yatimah Alias, Khalijah Awang, A. Hamid A. Hadi, Odile Thoison, Thierry Sevenet, M. Pais, (1995), An Antimitotic and cytotoxic chalcone from *Fissistigma lanuginosum*, J. Nat. Prod., 58(8), 1160-1166.

59. Khalijah Awang, Thierry Sevenet, Mary Pais, A. Hamid A. Hadi, C. Kan-Fan, J-C. Quirion, F. Remy, H. Schaller, L.E.Teo, (1994), A Preliminary Chemotaxonomic Review of *Kopsia* (Apocynaceae), Journal of Ethnopharmacology, 41(3), 147-183.

60. Khalijah Awang, Odile Thoison, A. Hamid A. Hadi, Mary Pais and Thierry Sevenet, (1993), Alkaloids from *Kopsia singapurensis*, Nat. Prod. Letters, 3(4), 283-289.

61. Khalijah Awang, Thierry Sevenet Mary, M. Pais, A. Hamid A. Hadi, (1993), Alkaloids of *Kopsia lapidilecta*, J. Nat. Prod., 56(7), 1134-1139.

62. Khalijah Awang, Thierry Sevenet Mary, M. Pais, A. Hamid A. Hadi, (1992), Lapidilectine A and Lapidilectine B, two new alkaloids from *Kopsia lapidilecta*, Tetrahedron Letters, 33(18), 2493-2496.

63. K. Awang, M. Pais, T. Sevenet, H. Schaller, A.M. Nasir, A. Hamid A. Hadi, (1991), "Eburnaminol and larutensine, two indole alkaloids from *Kopsia larutensis*", Phytochemistry, 30(9), 3164-3167.

Drug Discovery : the Search for the 'Magic Molecules'

Our tropical rainforest is one of the world's twelve mega biodiversity. Not only it is immensely rich in its species diversities but it is also one of the oldest in the world[1]. Its richness in diversity can be observed from the number of species that it has as compared to the Chinese and Indonesian flora (Table 1). Our rainforest is the home of 15,000 known flowering plants species while Indonesia has 20,000 species and China has 30,000 species respectively. Although the number of species we have is the least but our rainforest has the most number of species per sq. km. as compared to both Indonesia and China (Table 1).

Table 1 : Number of flowering plant species in Malaysia, Indonesia and China

Country	Total Land Area	No. of species (sq. km)	No. of species/ sq. km
Malaysia	329,847	15,000	0.045
Indonesia	1.9 million	20,000	0.011
China	9.6 million	30,000	0.0031

Every year thousands of tourists, amongst them are scientists from numerous research institutions and pharmaceutical industries visit our rainforests. Most of them flew thousands of miles to enjoy and explore the exotic tropical beauty of our flora and fauna. However, some of the 'scientific tourists' are interested in the substances that reside in our plants; the so called 'natural products' and their biological activities. Plants are actually the natural producers of chemical compounds and, indeed, they are very efficient manufacturers. Molecules synthesized by them are highly diversed in structure. These molecules (natural products) may be possible candidates for drug development.

These candidates are called 'lead compounds'. They will be used as templates to design potential drugs. The final molecule/s developed to be used therapeutically and commercialized will then be called 'medicines' or therapeutic agents or drugs. Some lead compounds are also medicine for example taxol **1**. In this talk, the 'magic molecules' refer to both lead compounds and medicines. Some examples

of therapeutic agents/ medicines from plants are taxol **1**, a compound from *Taxus brevifolia* Nutt., that is used to treat various types of cancer (lung, ovarian, breast) and morphine **2**, the infamous alkaloid which is one of the best analgesic agent ever known to human race.

An example of a compound from our Malaysian flora that is on the path to be called a 'medicine' is calanolide A **3**. It was isolated from the the plant *Calophyllum lanigerum var austrocoriaceum*, a very rare species from the mangosteen family.

The plant was originally screened for anti-cancer activity by the National Cancer Institute (NCI), USA but no significant activity was found (1987). Four years later, the NCI scientists found that a preparation from this tree is effective against the human immunodeficiency virus type 1 (HIV-1). Today it is under clinical study. Twenty years have passed and a molecule from our flora is finally on its path to be called a medicine. This discovery, unfortunately, did not involve any Malaysian institutions. It was an independent effort by the NCI of USA. Although the state of Sarawak might receive some financial benefit, there is no gain in terms of technology and scientific knowledge transfer as we, Malaysians, are not involved in the drug development process.

Realising the possible occurence of such incidents, University Malaya has formed a collaboration with the Institut de Chimie des Substances Naturelles (ICSN, CNRS) to screen and develop possible molecule candidates to be developed as a 'medicine'. This collaboration started officially in 1983 and it continues until today. An example of a 'lead compound' discovered in our collaboration is rhazinilam **4**, a seco indole alkaloid, that acts on tubulin similar to taxol **1**, taxotere, vinblastine and vincristine; drugs used to treat various types of cancer. Rhazinilam **4** exhibits an interesting mechanism of action: it induces a nonreversible assembly of tubulin as is observed in vinblastine and it inhibits the cold-induced disassembly of the microtubules similar to taxol.

The structure-activity relationship study (SAR) [2] and Quantitative Structure Activity studies (QSAR) on rhazinilam **4** was executed. More than thirty analogues were synthesized and hemisynthesized, unfortunately none is significantly more

potent than rhazinilam **4** [3]. At the moment, efforts on rhazinilam **4** and its analogues still continue and stemming from this research we have also attempted the synthesis of indoles which resulted in the discovery of a new path to indoles via acetamidostilbenes [4, 5].

The discovery of rhazinilam **4** has inspired our group to intensify our search for other 'magic molecules'. Chemotaxonomic and bioassay guided studies on selected Malaysian plants were actively pursued. Plants from various families were studied; Annonaceae, Apocynacea, Lauraceae, Meliaceae and Rubiaceae. Some of the chemical entities identified were erythrocarpin 5 (anti-tumour, P-388) from Chisocheton erythrocarpus [6], pedicin 6 (anti-tubulin) from *Fissistigma lanuginosum* [7] and meiogynine **7** (anti-tumour, KB cells) from *Meiogyne cylindrocarpa* [8].

The isolation and purification of these natural products or lead compounds are not at all a trivial task. It involves meticulous application of extraction and chromatographic techniques (CC, TLC, HPLC, UPLC). The 'hunt' for the bioactive molecules responsible for the bioactivities is much more difficult and many at times the efforts met with failures. Sensitive spectroscopic techniques and high performance equipments are employed to elucidate the structures of the isolated compounds (NMR, HRMS). Fig. 1 shows the 1H NMR spectrum of a mixture of two prenylated coumarins and Fig. 2 shows the LC MS-MS profile of this mixture. The structures of both compounds, 5,7-dihydroxy-8-(2-methylbutanoyl)-6-[(E)-3,7-dimethylocta-2,6-dienyl]-4-phenyl-2H-chromen-2-one **8** and 5,7-dihydroxy-8-(3-methylbutanoyl)-6-[(E)-3,7-dimethylocta-2,6-dienyl]-4-phenyl-2*H*-chromen-2-one **9**, were unraveled by using both high resolution NMR and UPLC-MS-MS analysis [9].

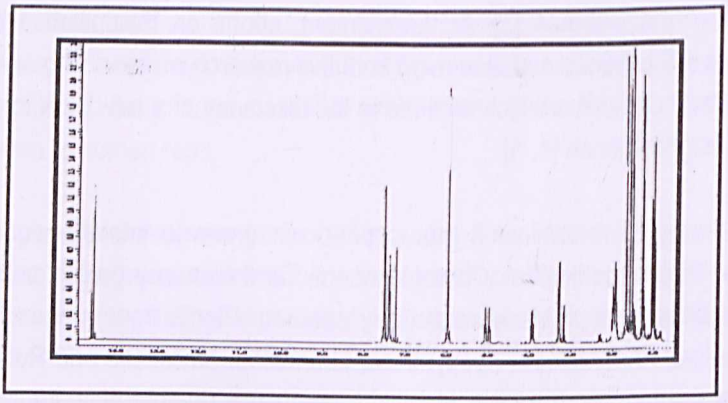


Fig. 1 : 1H NMR spectrum of a mixture of two prenylated coumarins

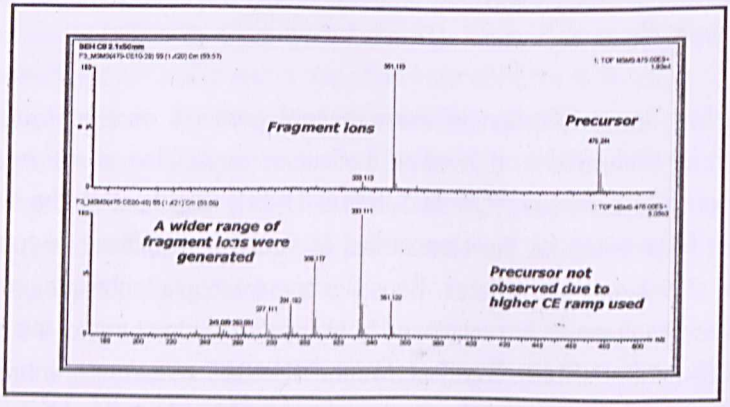


Fig. 2 : LC MS-MS profile of a mixture of two prenylated coumarins

The knowledge acquired from our ventures in this collaboration have resulted in the discovery of many lead compounds but not yet, a clinically used compound – medicine. The process to get a 'medicine' usually takes a long time and very costly (~ 1 billion US dollar). Undeniably, luck is a very important factor. The moment of encounter with the 'magic molecule/s' that could satisfy the specifications of pharmaceutical industries and later used as a medicine is not known, but efforts must be continued and God willing (insyaallah), finally we shall meet the day.

I began to ponder, with the knowledge acquired, on the type of research activity that could give more direct benefits to humanity, in particular our own society.

Many years have been spent for the search of the 'magic molecules' from the remote tropical jungles. I then realized that I have actually forgotten to look at the plants easily accessable to us in our everyday lives; our own medicinal plants used in jamu, sensei and ayurvedic medicines.

Our forefathers used 'akar kayu' and herbs to treat and prevent various ailments. In fact some of these plants are taken in our daily food in the form of 'ulam' or added in our soup or curry. Today such practice and knowledge is fast evading us as we, the present generation, seems to forget these valuable heritage. Modern medicines and 'fast foods' is the culture practiced by most of the young generation today. As our Malaysian society becomes more educated and modern, the belief in the use and practice of traditional medicines and herbs is eroding as these knowledge lacks scientific evidence. Even if there is some scientific evidence, most of the chemical and biological studies on our medicinal plants were done in China, India, Japan and Indonesia as these plants also grow in these countries. However, studies by Malaysians are still scarce.

Realising this I started collaborations with colleagues from ISB and Medical Faculty to study the chemical entities and the biological activities of our medicinal plants. I shall discuss briefly the findings from two plants in particular; *Kaempheria galangal* (cekur) and *Andrographis panicula* (hempedu bumi).

Kaempheria galanga (cekur), grows wild or cultivated in India, China and South East Asia [10]. It is widely used as flavouring in food. In Malaysia and Indonesia it is a compulsory ingredient of the 'pecal' sauce. It is an important component in 'jamu' preparations especially for the treatment of swelling and muscular rheumatism. It is also known to treat ailments such as hypertension and asthma [11, 12].

Our group has embarked on a bioassay guided study of the dichloromethane extract of the rhizome which has led to the isolation and characterization of ethyl cinnamate (EC) **10**. We have shown that EC has a similar vasorelaxant action to verapamil, a calcium channel blocker. This finding may explain the use of this plant in treating hypertension [13, 14].

Andrographis panicula or hempedu bumi is widely cultivated in Southern Asia. This plant is native to India and Sri Lanka and is used in Ayurvedic systems of medicine. Our group has found that its hexane, dichloromethane and water extracts could cause coronary vasodilation since they reduces the coronary perfusion pressure. Six diterpenes were isolated and identified, andrographolide **11** being the major compound. All six compounds reduces coronary perfusion pressure. This finding also supports the traditional use of this plant in the treatment of hypertension.

The compounds mentioned above are the molecules that we could consume orally when the plant parts (rhizome, fruits, leaves, barks) are added in medicinal preparations or cookings. Another type of molecule that could help cure ailments and release physical and mental tensions are the volatiles that we inhale. These are molecules that are used in aromatherapy and perfumery/flavouring industries. Interests in this area has brought me to the studies of essential oils and volatiles of our fragrant plants. My first study was on Plumeria species, known locally as kemboja or pokok kubur. The flowers impart vey subtle and soft aroma that is very relaxing. The oils of their flowers contain many monoterpenes, sesquiterpenes and aromatic compounds that are responsible for the soothing aroma they impart [15, 16].

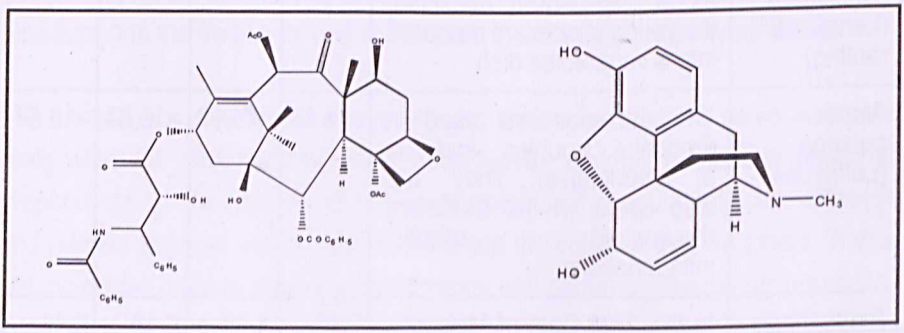
Recently, my group has reported the essential oils from two Zingiberaceae species: *Elattariopsis curtisii* and *Alpinia conchigera* [17, 18]. *Elattariopsis curtisii*, known locally as 'pijat pijat', is sometimes used as 'gulai' ingredient in Kelantan. *Alpinia* conchigera, also known as lengkuas ranting, is used in post-partum medicine and the treatment of fungal infections. The former produces oils that contain mainly aliphatic alcohols and aldehydes while the latter produces mainly 1,8-cineole **12** and β-bisabolene **13**. Essential oils from both plants have shown moderate antibacterial and antifungal properties. Our group has also performed antimicrobial testings on the essential oils of selected herbs and spices that are added in our soups, curries and gulai. Table 2 showed that most of them impart volatiles that are beneficial to our health as they possess anti-microbial agents.

Table 2 : Anti-bacteria activities of essential oils of selected Malaysian herbs (Rhizome)

Species	Medicinal usage	Antimicrobial activity			
		Pa	Pce	Sa	Se
Alpinia conchigera (Lengkuas ranting)	The rhizomes are consumed as a post-partum medicine; the young shoots are prepared into a vegetables dish.	>33.33	>33.33	>33.33	>33.33
Alpinia galanga (Lengkuas)	The rhizomes are used in bronchial troubles and as a carminative. They are also useful in the treatment rheumatoid arthritis, inflammations.	>16.67	>16.67	>16.67	>16.67
Elettariopsis curtisii (Pijat-pijat)	In the East Cost of Malaysia, people used the rhizomes in their curry as appetizer.	2.43	4.86	6.48	6.48
Elettaria cardamomum (Buah pelaga) - seeds	Flavour in food.	8.34	16.67	16.67	8.34
Kaempferia galanga (Cekur)	Flavour in food.	8.34	16.67	16.67	8.34
Zingiber officinale (Halia bara)	Flavour in food.	7.45	14.89	14.89	14.89
Zingiber officinale (Halia padi)	Flavour in food.	14.89	14.89	14.89	14.89
Streptomycin sulphate	-	**1.74**	**1.74**	**3.48**	**3.48**

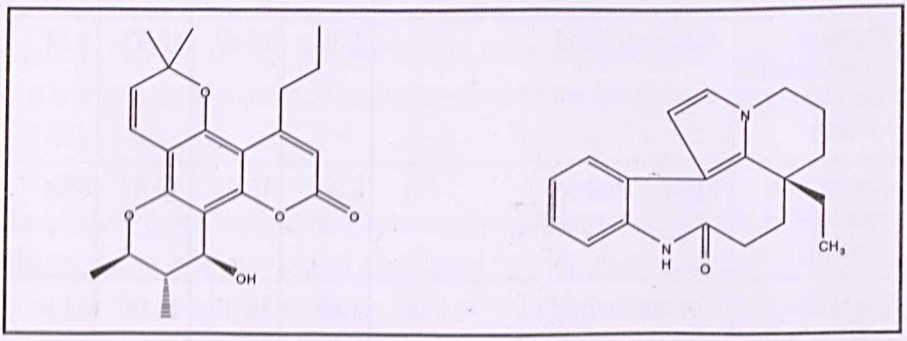
Pa : Pseudomonas aeruginosa
Pce : Pseudomonas cepasia
Sa : Staphylococcus aureus
Se : Staphylococcus epidermidis

Therefore, from our gardens and backyards, we actually could find, taste and feel these 'magic molecules' which are beneficial to our health; physical and mental wellbeing. They may not be the 'magic molecules' to the pharmaceutical giants but they are to all of us as our health is the crown of our life and beyond any material quantification.



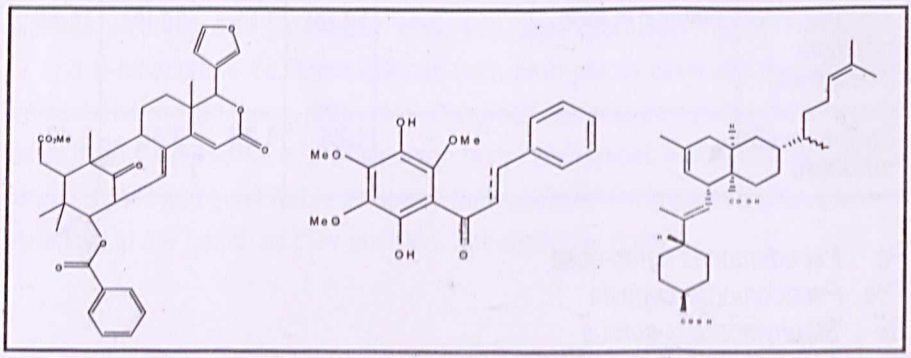
Taxol **1**

Morphine **2**



Calanolide **3**

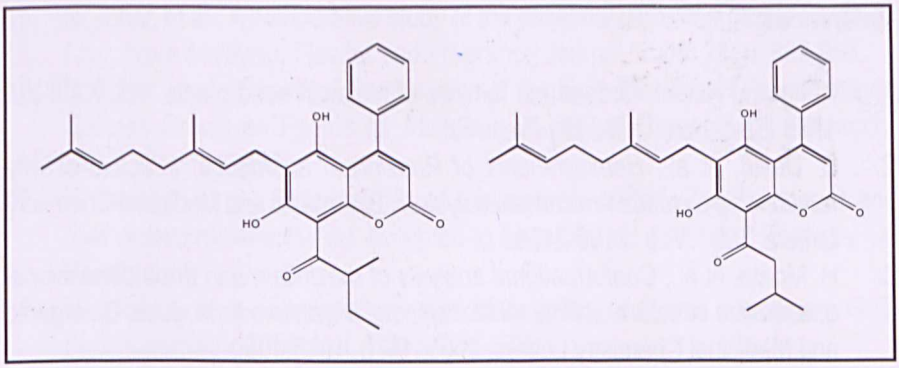
Rhazinilam **4**



Erythrocarpin **5**

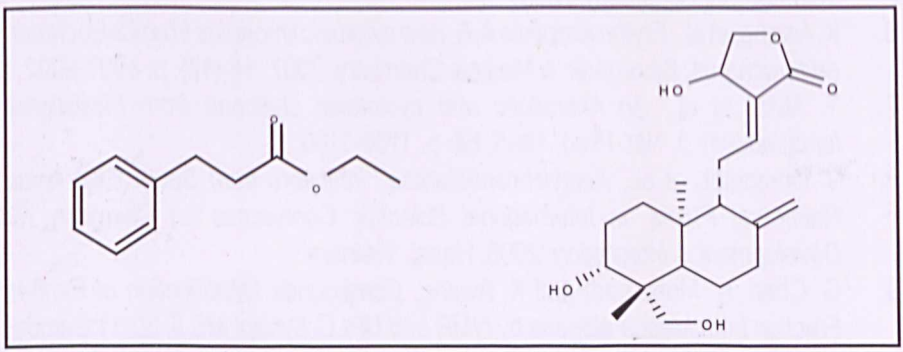
Pedicin **6**

Meiogynine **7**



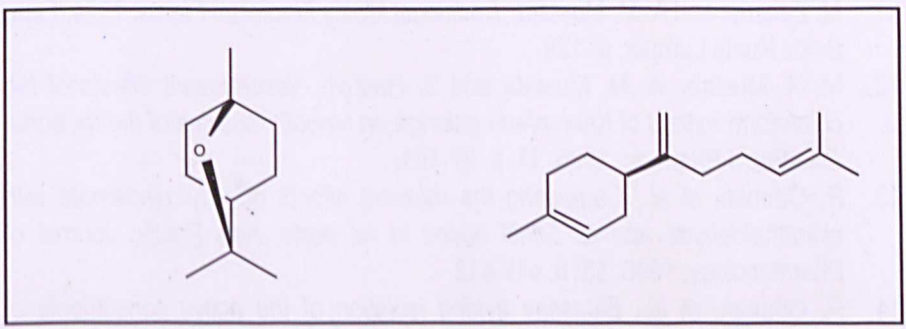
5,7-dihydroxy-8-(2-methylbutanoyl)-6-[(E)-3,7-dimethylocta-2,6-dienyl]-4-phenyl-2H-chromen-2-one
8

5,7-dihydroxy-8-(3-methylbutanoyl)-6-[(E)-3,7-dimethylocta-2,6-dienyl]-4-phenyl-2H-chromen-2-one
9



Ethyl cinnamate **10**

Andrographolide **11**



1,8- cineole **12**

β -bisabolene **13**

References:

1. Keng and Hsuan. Orders and families of Malayan seed plants. Vol. XXIII-XL. 1978: Singapore University Press Ed.
2. B. David, et al., *Hemisynthesis of Rhazinilam analogues: structure-activity relationship on tubulin-microtubule system.* Bioorganic and Medicinal Chemistry Letters, 1997. 7: p. 2155-2158.
3. H. Morita, et al., *Conformational analysis of rhazinilam and three dimensional quantitative structure-activity relationships of rhazinilam analogues.* Bioorganic and Medicinal Chemistry Letters, 2005. **15**: p. 1045-1050.
4. N. F.Thomas, et al., *A tandem highly stereoselective FeCl3 – promoted synthesis as a bisindoline; synthetic utility of radical cations in heterocyclic conscytuction.* Tetrahedron, 2004. **60**: p. 11733- 11742.
5. K. Ahmad, et al., *A FeCl3-promoted highly atropodiastereoselective cascade reaction: Synthetic utility of radical cations in indolostilbene construction.* Tetrahedron(Accepted), 2008.
6. K. Awang, et al., *Erythrocarpines A-E, new cytotoxic limonoids from Chisocheton erythrocarpus.* Bioorganic & Medical Chemistry, 2007. **15 (17)**: p. 5997-6002.
7. Y. Alias, et al., *An Antimitotic and cyctotoxic chalcone from Fissistigma lanuginosum.* J. Nat. Prod, 1995. **58**: p. 1160-1166.
8. V. Dumontet, et al., *Acetylcholinesterase inhibitors from South East Asian Rainforest Plants, in International Scientific Conference on Chemistry for Development & Integration.* 2008: Hanoi, Vietnam.
9. G. Chan, K. Mohamad, and K. Awang, *Compounds Identification of Purified Fraction from Mesua elegans by NMR and UPLC-Synapt MS II.* 30-31 October 2008, International Seminar on Chemistry 2008, Bandung, Indonesia.
10. RE, Holltum, *The Zingiberaceae of the Malay Peninsula*, Gard Bull Sing, 1950. 13: p. 117-123.
11. M. Zakaria, and A. M. Mustafa, *Traditional Malay Medicinal Plants.* 1994, Fajar Bakti: Kuala Lumpur. p. 129.
12. M. R. Mustafa, A. M. Mustafa and S. Hashim, *Vasorelaxant effects of the chloroform extract of Kaempferia galanga on smooth muscles of the rat aorta.* Asia Pac J Pharmac, 1996. **11**: p. 97-101.
13. R. Othman, et al., *Comparing the relaxant effects of ethyl cinnamate with cinnamaldehyde and its Schiff bases in rat aorta.* Asia Pasific Journal of Pharmacology, 1998. **13**: p. s17-s18.
14. R. Othman, et al., *Bioassay gyided isolation of the active constituents of Kaempferia galanga on constricted smooth muscleof rat aorta.* Phytomedicine, 2006. **13**: p. 61-66.

15. N. Tohar, et al., *A comparative study of the essential oils of the genus Plumeria Linn. From Malaysia*. Flavour and Fragrance Journal, 2006. **21**: p. 859-863.
16. N. Tohar, et al., *Chemical Composition of the Essential Oils of Four Plumeria Species Grown on Peninsular Malaysia*. Journal of Essential Oil Research, 2006. **18:** p. 613-617.
17. H. Ibrahim, et al., *Essential oils of Elettariopsis curtisii (Zingiberaceae) and their antimicrobial activities*. accepted to be published Journal of Essential Oil Research.
18. H. Ibrahim, et al., *Essential oils and Bioactivities of Alpinia conchigera Griff.* Food Chemistry, 2009. **Vol. 113**: p. 575-577.