

CHAPTER 4

CONCLUSION

In this study, the CH₂Cl₂ crude extract of the roots of *Maytenus mekongensis* was investigated. Eight new alkaloids were isolated and identified as 7-*epi*-euojaponine A (**XIII**), 2-*O*-benzoyl-2-deacetylmayteine (**XIV**), 7-*epi*-5-*O*-benzoyl-5-deacetylperitassine A (**XV**), mekongensine (**XVI**), 7-*epi*-mekongensine (**XVII**), 1-*O*-benzoyl-1-deacetylmekongensine (**XVIII**), 9'-deacetoxymekongensine (**XIX**), 1-*O*-benzoyl-1-deacetyl-9'-deacetoxymekongensine (**XX**) together with four known alkaloids euonymine (**IX**), 7-*epi*-euonymine (**X**), mayteine (**XI**), and 7-*epi*-mayteine (**XII**), eight known triterpenes, abruslactone A (**I**), 3 β ,29-dihydroxyolean-12-en (**II**), 3 β -hydroxyolean-12-en-29-oic acid (**III**), polpunonic acid (**IV**), salaspermic acid (**V**), cangoronine (**VI**), 3-hydroxy-2-oxofriedelan-3-ene-20 α -carboxylic acid (**VII**), and tingenone (**VIII**) were also isolated.

The isolated alkaloids were evaluated for their cytotoxic, antiplasmodial and antituberculous activity. Compounds **XVI-XX** exhibited antiplasmodial activity against *Plasmodium falciparum* with IC₅₀ values of 2.86, 3.60, 3.46, 2.74 and 2.33 μ g/mL respectively. Only compounds **XVI** and **XIX** showed very weak cytotoxic activity against human mouth epidermal carcinoma (KB) cell line with IC₅₀ values of 28.2 and 46.7 μ g/mL, respectively, and no inhibitory activity was observed with other cell lines.

Compound **XVI** was evaluated for its antimycobacterial activity against *Mycobacterium tuberculosis* H37Ra and showed no activity at 200 $\mu\text{g/mL}$.



REFERENCES

1. Schaneberg, B. T., D. K. Green, and A. T. Sneden. 2001. Dihydroagarofuran sesquiterpene alkaloid from *Maytenus putterlickoides*. **J. Nat. Prod.** 64: 624-626.
2. Chávez, H., E. Valdivia, A. Estévez-Braun, and A. G. Ravelo. 1998. Structure of new bioactive triterpenes related to 22- β -hydroxy-tingenone. **Tetrahedron** 54: 13579-13590.
3. Alvarenga, N. L., C. A. Velazquez, R. Gomez, N. J. Canela, I. L. Bazzocchi, and E. A. Ferro. 1999. A New antibiotic nortriterpene quinone methide from *Maytenus catingarum*. **J. Nat. Prod.** 62: 750-751.
4. Nunez, M. J., A. Guadano, I. A. Jimenez, A. G. Ravelo, A. Gonzalez-Coloma, and I. L. Bazzocchi. 2004. Insecticidal sesquiterpene pyridine alkaloids from *Maytenus chiapensis*. **J. Nat. Prod.** 67: 14-18.
5. González, A. G., I. A. Jiménez, A. G. Ravelo, J. G. Sazatornil, and I. L. Bazzocchi. 1993. New sesquiterpenes with antifeedant activity from *Maytenus canariensis* (Celastraceae). **Tetrahedron** 49: 697-702.
6. Kupchan, S. M., Y. Komoda, A. R. Branfman, A. T. Sneden, W. A. Court, G. J. Thomas, H. P. J. Hintz, R. M. Smith, A. Karim, G. A. Howie, A. K. Verma, Y. Nagao, R. G. Dailey, V. A. Zimmerly, Jr., and W. C. J. Sumner. 1977. The maytansinoids. Isolation, structural elucidation, and chemical interrelation of novel ansa macrolides. **J. Org. Chem.** 42: 2349-2357.
7. Smitinand, T. 1980. **Thai Plant Names (Botanical names-Vernacular names)**.

Bangkok: Funny.

8. De Sousa, J. R., J. A. Pinheiro, E. F. Ribeiro, E. De Sousa, and J. G. S. Maia. 1986. A Sesquiterpene evoninoate alkaloid from *Maytenus guianensis*. **Phytochemistry** 25: 1776-1778.
9. Kuo, Y. H., C.-H. Chen, and L.-M. Y. Kuo. 1990. Antitumor agents, 112. ¹ emarginatine B, a novel potent cytotoxic sesquiterpene pyridine alkaloid from *Maytenus emarginata*. **J. Nat. Prod.** 53: 422-428.
10. Itokawa, H., O. Shiota, H. Morita, K. Takeya, and Y. Iitaka. 1993. Isolation, structural elucidation and conformational analysis of sesquiterpene pyridine alkaloids from *Maytenus ebenifolia* Reiss. X-ray molecular structure of ebenifoline W-I. **J. Chem. Soc. Perkin Trans. 1**: 1247-1254.
11. Shiota, O., A. Otsuka, H. Morita, K. Takeya, and H. Itokawa. 1994. Sesquiterpene pyridine alkaloid from *Maytenus chuchuhuasca*. **Heterocycle** 38: 2219-2229.
12. Kuo, Y.-H., C.-H. Chen, M.-L. King, T.-S. Wu, and K.-H. Lee. 1994. Sesquiterpene pyridine alkaloid from *Maytenus emarginata*: Emarginatine-C and -D and cytotoxic emarginatine-E and emarginatinine. **Phytochemistry** 35: 803-807.
13. Kuo, Y.-H., M.-L. King, C.-F. Chen, H.-Y. Chen, C.-H. C. Chen, K. Chen, and K.-H. Lee. 1994. Two new macrolide sesquiterpene pyridine alkaloids from *Maytenus emarginata*: emarginatine G and the cytotoxic emarginatine F. **J. Nat. Prod.** 57: 263-269.
14. Kuo, Y.-H., and J.-C. Ou. 1995. A new triterpene lactone, Maytenfolone, and a new sesquiterpene pyridine alkaloid, emarginatine H, from the leaves of *Maytenus diversifolia*. **J. Nat. Prod.** 58: 1103-1108.
15. Corsino, J., V. da S. Bolzani, A. M. S. Periera, S. C. Franca, and M. Furlan.

1998. Bioactive sesquiterpene pyrdine alkaloids from *Maytenus aquifolium*. **Phytochemistry** 48: 137-140.
16. Corsino, J., V. da S. Bolzani, A. M. S. Periera, S. C. Franca, and M. Furlan. 1998. Further sesquiterpene pyrdine alkaloids from *Maytenus aquifolium*. **Phytochemistry** 49: 2181-2183.
17. Schaneberg, B. T., D. K. Green, and A. T. Sneden. 2001. Dihydroagarofuran sesquiterpene alkaloid from *Maytenus putterlickoides*. **J. Nat. Prod.** 64: 624-626.
18. Nakagawa, H., Y. Takaishi, Y. Fujimoto, C. Duque, C. Garzon, M. Sato, M. Okamoto, and S. U. Ahmed. 2004. Chemical constituents from the Colombian medicinal plant *Maytenus laevis*. **J. Nat. Prod.** 67: 1919-1924.
19. De Almeida, M. T. R., C. Ríos-Luci, J. M. Padrón, and J. A. Palermo. 2010. Antiproliferative terpenoids and alkaloids from the roots of *Maytenus vitis-idaea* and *Maytenus spinosa*. **Phytochemistry** 71: 1741-1748.
20. Nazaki, H., H. Suzuki, K. H. Lee, and A. T. McPhail. 1982. Structure and stereochemistry of maytenfolic acid and maytenfoliol, two new antileukemic triterpenes from *Maytenus diversifolia*: X-ray crystal structures. **J. Chem. Soc., Chem. Commun.:** 1048-1051.
21. Lee, K.-H., and H. Nazaki. 1984. Structure and stereochemistry of maytensifolin-A, a novel hydroperoxy-nortriterpene from *Maytenus diversifolia*. **Tetrahedron Lett.** 25: 707-710.
22. González, A. G., E. A. Ferro, and A. N. Ravelo. 1987. Triterpenes from *Maytenus Horrida*. **Phytochemistry** 26: 2785-2788.

23. Itokawa, H., O. Shirota, H. Ikuta, H. Morita, K. Takeya, and Y. Iitaka. 1991. Triterpenes from *Maytenus ilicifolia*. **Phytochemistry** 30: 3713-3716.
24. González, A. G., I. A. Jiménez, and A. G. Ravelo. 1992. Triterpenes from *Maytenus canariensis* and synthesis of a derivative from betulin. **Phytochemistry** 31: 2069-2072.
25. Shirota, O., H. Morita, K. Takeya, H. Itokawa, and Y. Iitaka. 1994. Cytotoxic aromatic triterpenes from *Maytenus ilicifolia* and *Maytenus chuchuhuasca*. **J. Nat. Prod.** 57: 1675-1681.
26. González, A. G., N. L. Alvarenga, A. G. Ravelo, J. G. Sazatornil, and I. L. Bazzocchi. 1995. Two triterpenes from *Maytenus canariensis*. **J. Nat. Prod.** 58: 570-573.
27. González, A. G., N. L. Alvarenga, A. G. Ravelo, I. A. Jiménez, I. L. Bazzocchi, N. J. Canela, and L. M. Moujir. 1996. Antibiotic phenolic nor-triterpenes from *Maytenus canariensis*. **Phytochemistry** 43: 129-132.
28. González, A. G., N. L. Alvarenga, A. G. Ravelo, I. L. Bazzocchi, E. A. Ferro, A. G. Navarro, and L. M. Moujir. 1996. Scutione, a new bioactive norquinone methide triterpene from *Maytenus scutioides* (Celastraceae). **Bioorg. Med. Chem.** 4: 815-820.
29. Shirota, O., T. Tamemura, H. Morita, K. Takeya, and H. Itokawa. 1996. Triterpenes from Brazilian medicinal plant "Chuchuhuasi" (*Maytenus krukovii*). **J. Nat. Prod.** 59: 1072-1075.
30. Chávez, H., A. Estévez-Braun, A. G. Ravelo, and A. G. González. 1997. First examples of dammarane triterpenes isolated from Clastraceae. **Tetrahedron** 53: 6465-6472.

31. Chávez, H., A. Estévez-Braun, A. G. Ravelo, and A. G. González. 1998. Friedelane triterpenoids from *Maytenus macrocarpa*. **J. Nat. Prod.** 61: 82-85.
32. Chávez, H., E. Valdivia, A. Estévez-Braun, and A. G. Ravelo. 1998. Structure of new bioactive triterpenes related to 22- β -hydroxy-tingenone. **Tetrahedron** 54: 1357-1359.
33. Chávez, H., A. Estévez-Braun, A. G. Ravelo, and A. G. González. 1999. New phenolic and quinone-methide triterpenes from *Maytenus amazonica*. **J. Nat. Prod.** 62: 434-436.
34. Chávez, H., G. Rodríguez, A. Estévez-Braun, A. G. Ravelo, R. Estévez-Reyes, A. G. González, J. L. Fdez-Puente, and D. García-Grávalos. 2000. Marcrocarpins A-D, new cytotoxic nor-triterpenes from *Maytenus macrocarpa*. **Bioorg. Med. Chem. Lett** 10: 759-762.
35. Muhammad, I., K. A. El Sayed, J. S. Mossa, M. S. Al-Said, F. S. El-Ferally, A. M. Clark, C. D. Hufford, S. Oh, and A. M. S. Mayer. 2000. Bioactive 12-oleanene triterpene and secotriterpene acids from *Maytenus undata*. **J. Nat. Prod.** 63: 605-610.
36. Ohsaki, A., Y. Imai, M. Naruse, S.-I. Ayabe, K. Komiyama, and J. Takashima. 2004. Four new triterpenoids from *Maytenus ilicifolia*. **J. Nat. Prod.** 67: 469-471.
37. Feng, X., Z. Gao, S. Li, S. H. Jones, and S. M. Hecht. 2004. DNA polymerase β lyase inhibitors from *Maytenus putterlickoides*. **J. Nat. Prod.** 67: 1744-1747.
38. Núñez, M. J., C. P. Reyes, I. A. Jiménez, L. Moujir, and I. L. Bazzocchi. 2005. Lupane triterpenoids from *Maytenus* species. **J. Nat. Prod.** 68: 1018-1021.

39. Rodríguez, F. M., M. R. López, I. A. Jiménez, L. Moujir, A. G. Ravelo, and I. L. Bazzocchi. 2005. New phenolic triterpenes from *Maytenus blepharodes*. Semisynthesis of 6-deoxoblepharodol from pristimerin. **Tetrahedron** 61: 2513-2519.
40. Reyes, C. P., M. J. Núñez, I. A. Jiménez, J. Busserolles, M. J. Alcaraz, and I. L. Bazzocchi. 2006. Activity of lupane triterpenoids from *Maytenus* species as inhibitors of nitric oxide and prostaglandin E₂. **Bioorg. Med. Chem.** 4: 1573-1579.
41. Gutiérrez, F., A. Estévez-Braun, A. G. Ravelo, L. Astudillo, and R. Zárate. 2007. Terpenoids from the medicinal plant *Maytenus ilicifolia*. **J. Nat. Prod.** 70: 1049-1052.
42. Delgado-Méndez, P., N. Herrera, H. Chávez, A. Estévez-Braun, A. G. Ravelo, F. Cortes, S. Castanys, and F. Gamarro. 2008. New terpenoids from *Maytenus apurimacensis* as MDR reversal agents in the parasite *Leishmania*. **Bioorg. Med. Chem.** 16: 1425-1430.
43. Vazdekis, N. E., H. Chávez, A. Estévez-Braun, and A. G. Ravelo. 2009. Triterpenoids and a lignan from the aerial parts of *Maytenus apurimacensis*. **J. Nat. Prod.** 72: 1045-1048.
44. Oramas-Royo, S. M., H. Chávez, F. M. Rodríguez, L. Fernández-Pérez, and A. G. Ravelo. 2010. Cytotoxic triterpenoids from *Maytenus retusa*. **J. Nat. Prod.** 73: 2029-2034.
45. Skehan, P., R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney, and M. R. Boyd. 1990. New colorimetric cytotoxicity assay for anticancer-drug screening. **J. Natl. Cancer Inst.** 82:

1107-1112.

46. Trager, W., and J. B. Jensen. 1976. Human malarial parasites in continuous culture. **Science** 193: 673-675.
47. Desjardins, R. E., C. J. Canfield, J. D. Haynes, and J. D. Chulay. 1979. Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique. **Antimicrob. Agents Chemother.** 16: 710-718.
48. Mahato, S. B., and A. P. Kundu. 1994. ¹³C NMR Spectra of pentacyclic triterpenoids—A compilation and some salient features. **Phytochemistry** 37: 1517-1575.
49. Chang, H.-M., T.-C. Chiang, and T. C. W. Mak. 1982. Isolation and structure elucidation of abruslactone A: A new oleanene-type triterpene from the roots and vines of *Abrus precatorius* L. **J. Chem. Soc., Chem. Commun.** 1197-1198.
50. Nozaki, H., H. Suzuki, T. Hirayama, R. Kasai, R.-Y. Wu, and K.-H. Lee. 1986. Antitumour triterpenes of *Maytenus diversifolia*. **Phytochemistry** 25: 479-485.
51. Yong, J.-P., J.-W. Wang, H. A. Aisa, and L. J. Liu. 2008. Synthesis of glycyrrhetic acid derivatives. **Chem. Nat. Comp.** 44: 194-196.
52. Nozaki, H., Y. Matsuura, S. Hirono, R. Kasai, J.-J. Chang, and K.-H. Lee. 1990. Antitumor agent, 116. Cytotoxic triterpenes from *Maytenus diversifolia*. **J. Nat. Prod.** 53: 1039-1041.
53. Chen, K., Q. Shi, Y. Kashiwada, D.-C. Zhang, C. Q. Hu, J. Q. Jin, H. Nozaki, R. E. Kilkuskie, E. Tramontano, Y. C. Cheng, D. R. McPhail, A. T. McPhail, and K.-H. Lee. 1992. Anti-AIDS agents, 6. salaspermic acid, an anti-HIV

- principle from *tripterygium wilfordii*, and the structure-activity correlation with its related compounds. **J. Nat. Prod.** 55: 340-346.
54. Morota, T., C.-X. Yang, H. Sasaki, W.-Z. Qin, K. Sugama, K.-L. Miao, T. Yoshino, L.-H. Xu, M. Maruno, and B.-H. Yang. 1995. Triterpenes from *Tripterigium wilfordii*. **Phytochemistry** 39: 1153-1157.
55. Ngassapa, O., D. D. Soejarto, J. M. Pezzuto, and N. R. Farnsworth. 1994. Quinone-methide triterpenes and salaspermic acid from *Kokoona ochracea*. **J. Nat. Prod.** 57: 1-8.
56. Yamada, K., K. Sugiura, Y. Shizuri, H. Wada, and Y. Hirata. 1977. Isolation and structures of euonymine and neoeuonymine, alkaloids from *Euonymus sieboldiana* blume. **Tetrahedron** 33: 1725-1728.
57. Han, B. H., M. K. Park, J. H. Ryu, J. H. Park, and H. Naoki. 1990. Sesquiterpene alkaloids from *Euonymus japonica*. **Phytochemistry** 29: 2303-2307.
58. Klass, J., W. F. Tinto, W. F. Reynolds, S. McLean. 1993. Peritassines A and B, new sesquiterpene alkaloids from *Peritassa compta*. **J. Nat. Prod.** 56: 946-948.
59. Sekar, K. V. S., J.-M. Campagne, A. T. Sneden. 1996. 5-Benzoyl-5-deacetyl wilfordine: A new sesquiterpene nicotinoyl alkaloid from *Maytenus buchananii*. **Planta Med.** 62: 368-370.