

Separation of Camptothecin and 10-Hydroxycamptothecin from *Camptotheca acuminata* Decne and *Nothapadytes foetida* (Wight)

蕭景文、楊博文

E-mail: 9706982@mail.dyu.edu.tw

ABSTRACT

Camptothecin (CPT) is a compound isolated by Wall 's and others in 1966 from *Camptotheca acuminata* Decne. The derivatives of anti-cancer drugs camptothecin are products that have high economical. They are work on adenocarcinomas, prostate cancer, lung adenocarcinoma, ovary cancer, cervix cancer, AIDS, else. Camptothecin become the main anti-cancer drugs in the world. To extract camptothecin and 10-hydroxycamptothecin (10-OH-CPT), the traditional method usually waste time and solvent. The goals of this research is to find the best extraction method for obtaining camptothecin and 10-hydroxycamptothecin from *Camptotheca acuminata* Decne and *Nothapadytes foetida* (Wight) Sleum by using microwave-assisted extraction (MAE), ultrasonic-assisted extraction (UAE). Using high porous type resins HP-20, YPW-2, and HPA25 to separate camptothecin and 10-hydroxycamptothecin. The results showed high porous type resin YPW-2 had the best separation and purification effect.

Keywords : Camptothecin ; Microwave-assisted extraction ; Ultrasonic-assisted extraction ; Heating reflux- assisted extraction ; Separation ; Purification ; High porous type resins

Table of Contents

目錄 封面內頁 簽名頁 授權書iii 中文摘要iv 英文摘要v 誌謝vi 目錄vii 圖目錄xi 表目錄xiv 1. 緒論1 2. 文獻回顧3 2.1 喜樹鹼之簡介與現況3 2.2 喜樹之簡介5 2.3 喜樹藥理成分8 2.4 青脆枝之簡介8 2.5 青脆枝藥理成份10 2.6 喜樹鹼之抗癌機制11 2.7 喜樹鹼類藥物抗腫瘤應用現狀14 2.7.1 Irinotecan (CPT-11) 14 2.7.2 Topotecan (TPT) 14 2.7.3 9-nitrocamptothecin(9-NC) 和9-AC15 2.7.4 10-OH-CPT15 2.7.5 其他應用15 2.8 喜樹鹼之物化特性16 2.9 喜樹鹼衍生物及其結構效應關係18 2.10 微波輔助萃取技術(MAE)與其他傳統萃取技術方法之比較19 2.11 微波輔助萃取技術(MAE)之原理及應用21 2.12 大孔吸附樹脂在中藥成分分離中的應用22 2.13 大孔樹脂的性質及分離原理23 2.13.1 大孔吸附樹脂特性23 2.13.2 大孔吸附樹脂的預處理及再生24 2.14 大孔吸附樹脂在中藥成分研究中的應用24 2.14.1 黃酮(?)類25 2.14.2 皂?和其他?類25 2.14.3 生物鹼類25 2.14.4 其他25 3. 材料與方法28 3.1 實驗材料28 3.2 儀器設備28 3.3 藥品29 3.3.1 化學試藥29 3.3.2 樹脂29 3.3.3 標準品30 3.4 實驗設計與方法30 4. 結果與討論32 4.1 標準曲線的製備32 4.2 微波、熱迴流、超音波萃取效果之比較36 4.2.1 熱迴流萃取法，不同溶劑對於喜樹的萃取37 4.2.2 超音波萃取法，不同溶劑對於喜樹的萃取40 4.2.3 微波輔助萃取法，不同溶劑對於喜樹的萃取43 4.2.4 超音波萃取法，不同溶劑對於青脆枝的萃取46 4.2.5 微波輔助萃取法，不同溶劑對於青脆枝的萃取49 4.2.6 熱迴流、超音波、微波輔助萃取法對於萃取喜樹之總比較52 4.2.7 熱迴流、超音波、微波輔助萃取法對於萃取青脆枝之總比較54 4.2.8 兩階段萃取探討56 4.2.9 兩階段萃取喜樹、青脆枝結果59 4.2.10 兩階段萃取及一階段萃取的比較探討62 4.3 大孔吸附樹脂的分離純化66 4.3.1 大孔吸附樹脂的前處理66 4.3.2 大孔吸附樹脂分離純化的操作條件67 4.3.3 濃縮液經大孔吸附樹脂的分離純化67 4.3.4 HP-20大孔吸附樹脂對喜樹及青脆枝濃縮液的分離純化分析67 4.3.5 YPW-2大孔吸附樹脂對喜樹及青脆枝濃縮液的分離純化分析69 4.3.6 HPA25大孔吸附樹脂對喜樹及青脆枝濃縮液的分離純化分析73 5. 結論76 參考文獻78 附錄83

REFERENCES

1. 上海藥物研究所植物室喜樹研究組。1975。中草藥通。(5):17。
2. 王洋。2000。喜樹鹼生產工藝研究。東北林業大學博士學位論文。
3. 江蘇植物研究所編。1993。江蘇植誌。
4. 李立源、張冬?和白鳳武。2001。喜樹鹼及其衍生物的研究進展。大連民族學院學。3(2):02-0017。
5. 李國雄和王惠康。1995。喜樹鹼的化學及抗癌構效研究之最新進展。53 (1): 64-7。
6. 李興進。2004。青脆枝產業現況與發展研討會。
7. 邱年永和張光雄。1992。原色台灣藥用植物圖鑑(3)。
8. 邱年永和張光雄。1992。原色台灣藥用植物圖鑑(5)。
9. 耿寶琴。1995。紫杉醇類喜樹鹼類的研究進展。實用腫瘤雜誌。10(4): 199-201。
10. 張顯強、唐金剛和乙引。2004。中國喜樹資源及可持續開發對策。貴州師範大學學報(自然科學版)。22 (1)。
11. 張忠豪。2007。含抗癌藥喜樹鹼及10-羥基喜樹鹼之不同植物來源的萃取分析研究。大葉大學碩士學位論文。
12. 郭舜民。1994。喜樹鹼類似物的研究進展。國外醫學:藥學分冊。21 (5): 270-273。
13. 郭新娜和起彼得。1994。羥基喜樹鹼膀胱灌注合併高頻透熱治療膀胱癌近期療效觀察。軍醫進修學院院報。15(3): 182 14. 郭茵茹和李舒茵。1995。喜樹鹼抑制濾過光泡癰痕化的臨床研究。眼科研究。13(4): 262-264。
15. 焦敬榮和李習舜。1974。喜樹鹼二甲基石風溶液治療銀屑病的療效觀察。中華醫學雜誌。54(4): 208-210。
16. 黃瑞松、胡秋萍和陳燕軍。2004。應用均勻設計法優化喜樹果乙醇滲漉工藝條件。中國實驗方劑學雜誌。10(2):12-14。
17. 管志震。2000。羥基喜樹鹼的臨床療效評述[C]。200年全國腫瘤學術大會教育集。423-425。
- 18.

鄭武燦。2001。台灣植物圖鑑(上冊)。800。19. 劉業經、呂福原和歐辰雄。1994。台灣樹木誌。中興大學農學院出版委員會。925。20. 劉展眉。2002。用現代分離技術提取抗癌活性成分喜樹鹼的研究。廣東工業大學碩士學位論文。21. 顧德辛。1995。抗腫瘤藥物喜樹鹼及其類似物的研究開發。中國醫藥情報。1 (6): 340-344。22. Bleiberg, H. 1999. CPT-11 in gastrointestinal cancer. Eur J Cancer. 35(3): 371-379 23. Devanand, P.F. and Ramesh, K.S. 2005. Comparison of techniques for the extraction of the anti-cancer drug camptothecin from *Nothapodytes foetida*. Journal of chromatography A. 1063:9-13. 24. Donald, C. 1997. *Camptotheca acuminata*: China 's ' Tree of Joy ' Offers Hope in the U. S (Draft report). 25. Ejima, A. and Terasawa, H. 1992. Antitumor agents. V. synthesis and antileukemic activity of E-ring -modified-(RS)-camptothecin analogues, Chem Pharm Bull. 40(3):683-688. 26. Giovanella, B.C. and Hinz, H.R. 1991. Complete growth inhibition of human cancer xenografts in nude mice by treatment with 20-(S)-Camptothecin. Cancer Res. 51: 3052-3055. 27. Giovanella, B.C. and Stehlin, J.S. 1989. DNA topoisomerase I – targeted chemotherapy of human colon cancer in xenografts. Science. 246: 1046-1048. 28. Jew, S.S. and Kim, M.G. 1998. Synthesis and in vitro cytotoxicity of C(20)(RS)-camptothecin analogues modified at both B (or A) and E ring. Bioorg Med Chem Lett. 8(14):1797-1800. 29. James, J.S. 1997. Topotecan, CPT-11 (irinotecan), camptothecin and other topoisomerase inhibitors, AIDS Treatment News. in: www. imunet. org/ atn/ ZQX19701. html. 30. Jew, S.S. and Kim, M.G.. 1998. Synthesis and invitro cytotoxicity of C(20)(RS)-camptothecina analogues modified at both B (or A)and E ring. Bioorg Med Chem Lett. 8(14):1797-1800. 31. Kingsbury, W.D. and Boehm, J.C. Synthesis of water-soluble(aminoalkyl) camptothecin analogues: inhibition of topoisomerase I an dantitumor activity. 1991. J Med Chem. 34 (1):98-107. 32. Kingsbury, W.D., Herzberg, R.P. and Boehm, J.C. 1989. Chemical synthesis and structure activity Relationships related to SK&F 104864, a novel water-soluble analog of camptothecin. Proc Am Assoc Cancer Res. 30(3):62. 33. Li, Z. and Liu, Z. 2003. Effects of benzyladenine and naphthalene acetic acid on growth and camptothecin accumulation in *Camptotheca acuminata* seedlings. J Plant Growth Regul. 22:205-216. 34. Lin, L.Z. and Cordell, G.A. 1990. 19-O-methylangustoline from *Camptotheca acuminata*. phytochem. 29(8):2744-2746. 35. Matsuzaki, T. and Yokokura, T. 1988. Inhibition of spontaneous and experimental metastasis by a new derivative of camptothecin, CPT-11, in mice. Cancer Pharmacol. 21: 308-312. 36. Nakanishi, Y. and Takayama, K. 1999. Second-line chemotherapy with weekly cisplatin and irinotecan in patients with refractory lung cancer, Am J Clin Oncol. 22(4): 399-402. 37. Nicholas, A.W. and Wani, M.C. 1990. Plant antitumor agents.29 , Synthesis and biological activity of ring D and ring E modified analogues of camptothecin. J Med Chem. 33(3):972-978. 38. Priel, E. and Yosef, O. 1989. Detection of a novel DNA topoisomerase I activity associated with human immunodeficiency virus (HIV) and other retrovirus particles. International conference on Aids. 5, 586. 39. Priel, E.S. and Showalter, D. 1991. Inhibition of human-immunode ficiency virus (HIV-1), replication in vitro by noncytotoxicdoes of camptothecin, a topoisomerase-I inhibitor. AIDS Research and Human Rerroviruses. 7(1): 65-72. 40. Pantazis, P. and Han, Z. 1999. Water-insoluble camptothecin analogues as potential antiviral drugs. J Biomed Sci. 6(l):1-7. 41. Sawada, S. and Matsuoka, S.I. 1991. Synthesis and antitumor activity of 20(S)-camptothecin derivatives:A-ring modified and 7,10-disubstituted camptothecins. Chem Pharm Bull. 39(12):3183-318. 42. Sawada, S., Okajimas, and Alyama, R. 1991. Synthesis and antitumor activity of 20(S)-camptothecin derivatives: carbamat-linked, water-soluble derivatives of 7-ethyl-10hydroxycamptothecins. Chem Pharm Bull. 39(6):1446-1454. 43. Wani, M.C., Nicholas, A.W. and Wall, M.E. 1986. Plant antitumor agents.23. synthesis and antileukemic activity of camptothecinan alogues. J Med Chem. 29(11):2358-2363. 44. Wani, M.C. and Nicholas, A.W. 1987. Total synthesis and antileukemic activity of ring A substituted camptothecin analogues. Structure-activity correlations. J Med Chem. 30(10):1774-177. 45. Wani, M.C. and Nicholas, A.W. 1987. Total synthesis and antileukemic activity of ring A substituted camptothecin analogues. Structure-activity correlations. J Med Chem. 30(10):1774-1779. 46. Wall, M.E. and Campbell, H.F. 1972. Plant antitumor agens. X .the total synthesis of a ring DE analog camptothecin. J Amer Chem Soc. 94(10):3632-363.