DOI:10.5138/09750185.2228

AR JOURNALS ADVANCED RESEARCH

International Journal of Phytomedicine
2018;10(3):153-155

SHORT COMMUNICATION

Brevifoliol: An ignored cousin of Taxol

Fahad Mohammed AlRabae and Uzma Faridi*

Abstract

The discovery of paclitaxel, an anticancer agent was a milestone in the path of anticancer drug discovery. After approval from FDA taxol was widely used for cancer treatment. The taxol was isolated from the bark of fully grown taxus plants with is a fatal source, to overcome this problem almost all the species were investigated for the taxol and taxol like molecules. Brevifoliol is one of the many taxoid isolated from the taxus plants. The significance of brevifoliol was its source which was dried needles of plants including the Himalayan yew tree *Taxus wallichiana.* Brevifoliol belongs to the large group of diterpenoid cyclodecanes, the same group with which taxol belongs. In-vitro studies indicate that brevifoliol has significant activity against colon cancer cell line which is slightly better than taxol. In the present article, all the updated information and its superiority over taxol will be discussed.

Keywords: Brevifoliol; anticancer; taxoid; Taxus; Taxol; Cancer

Introduction

Taxoids are the large group of diterpenoid cyclodecanes. These are isolated from the genus Taxus and are known and used as anticancer agents. The first molecule from this group was Paclitaxel which was isolated in 1969 in very low amount (0.01 % yield) from the bark of Pacific yew, Taxus brevifolia [1]. The structure and the mechanism of action were confirmed in 1970s [2–4].

Taxol was one of the first anticancer drugs approved by the FDA to treat ovarian cancer and breast cancer [5].

Till date, More than 400 taxoids have been isolated from the Taxus genus [6–8]. Brevifoliol is also an investigational antitumor taxoid among a series of similar taxol derivatives by Balza F. et al in 1972 [9] . The molecule gained attention as it was isolated from the sustainable source, the needles of the Himalayan pacific yew tree and showed promising activity against many cell lines *in-vitro*.

Many in-vitro studies confirmed its anticancer properties in different human cancer cells like CaCo2 *in-vitro* and *in-silico* [10, 11]. Preliminary results clearly indicate that it could be the replacement of taxol as it shows significant activity against many cell lines and there are many drawbacks related to the isolation and toxicity of taxol.

Although preliminary studies showing promising results but still many studies are required to reach the final conclusion.

This mini-review summarizes the preclinical data and other published and unpublished reports and focuses on the clinical usefulness of this new agent in the treatment of cancer.

Drug Information

Brevifoliol was discovered by Balza and his team [9] from the needles of Taxus brevifolia (western yew) in a search for the replacement of taxol in low toxicity and more effectiveness. When it was isolated the structure was proposed as taxa-4(20),1 l-dienel/,Sa,7p,9%,1 O/l, 13x-hexaol-9a, IO/l-diacetate-7/I-benzoate) named as brevifoliol. After two years the revised structure was established by Georg *et al.* and Appendino *et al.* in 1993 [12–14] and they assigned its structure as 11(15/1)-abeo-taxa-4(20), 11-diene skeleton **(Figure 1).** After isolation from Taxus brevifolia, brevifoliol was isolated from other species of Taxus as well. In India it was isolated from the needles of the Himalayan yew *Taxus wallichiana* by Chattopadhyay et al in 2006 [11] .

* Correspondence: ufaridi@ut.edu.sa

Biochemistry Department, University of Tabuk, Saudi Arabia

Full list of author information is available at the end of the article.

Received: 18 Jan 2018, Accepted:01 May 2018

Isolation and solubility

Brevifoliol is an ample molecule (1.7 mg g- 1 fresh weight)) found in the needles of the Pacific yew Taxus brevifolia [15]*and can be* isolated from the ethanolic extract of the needles of Taxus brevifoliol and other Ta*xus* species which *is a* non-destructive mode of harvesting [9]. Another advantage associated with brevifoliol is the solubility in aqueous solvents. Taxol is not soluble in the water and other aqueous solvents.

Mechanism of Action

Brevifoliol exhibited anti-proliferative activity comparable with the paclitaxel against all the cell lines used,) brevifoliol showed significant activity against human colon cancer cell line, Caco2 which was comparatively higher than taxol [11]. Like taxol, brevifoliol binds with the microtubule and inhibits its depolymerisation **(figure 2 A and B)** (*In-silico and in-vitro*) [16]. The CaCo2 cells treated with brevifoliol were observed to be undergoing apoptosis through apoptosomes formation. Brevifoliol was observed to express the annexin V marker of apoptosis with low intensity of fluorescence, the indicator of late phase apoptosis. The nucleic acid was also fragmented providing ladder-like pattern due to the effect of brevifoliol. All the above-mentioned signs were the clear-cut indication of apoptosis **(Figure 2 C)** (unpublished data).

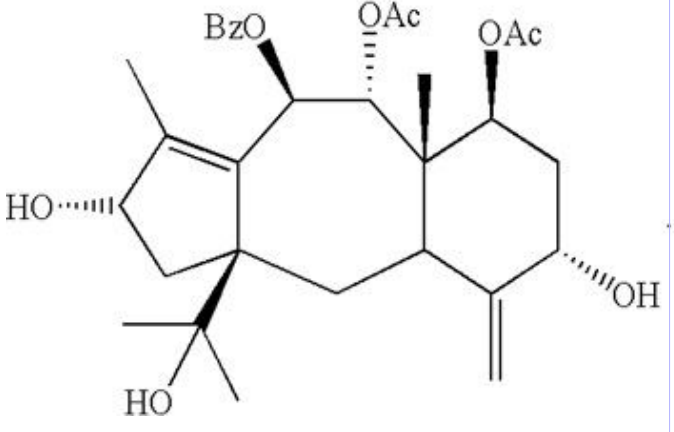

Figure 1 Structure of Brevifoliol

In order to compare the mechanism of action with that of paclitaxel was studied and it is observed that brevifoliol exhibited the same effect on microtubule dynamics as paclitaxel in terms of the tubulin polymerization pattern (). Therefore, these observations confirmed that the brevifoliol causes the tubulin polymerization as paclitaxel but it was not confirmed whether binding of brevifoliol is exactly similar to paclitaxel (unpublished data).

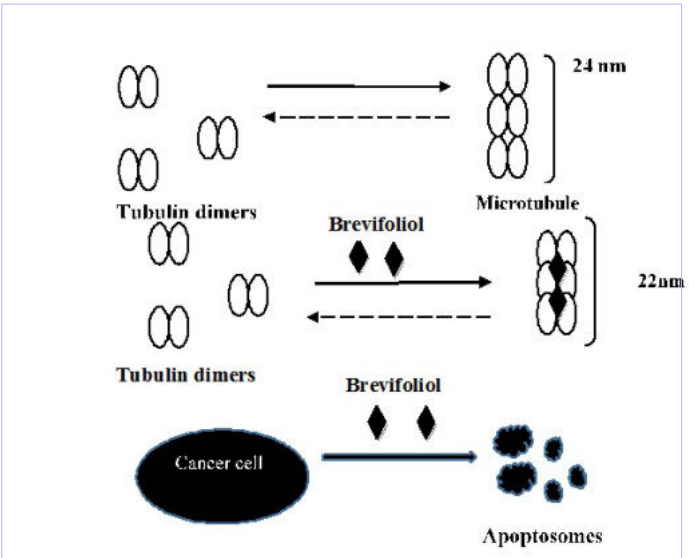

Figure 2 Probablemode of action of brevifoliol, normal tubulin polymerization anddepolymerisation (A), The probable binding of brevifoliol withmicrotubules (B)& the initiation of apoptosis in cancer cells inpresence of brevifoliol (C)

Derivatives of brevifoliol

Till now several derivatives of brevifoliol were synthesized and evaluated for the anticancer properties. [11, 17–19] Few of them showed significantly increased cytotoxicity in different human cancer cell lines. *In-silico* studies of derivatives of brevifoliol indicated that the importance of benzoate and acetate groups of brevifoliol as the removal of these groups makes brevifoliol inactive [16].

Future Prospects

Brevifoliol and its derivates have shown promising activity in *in-vitro* and *in-silico* studies. Some derivatives were showing better activity than paclitaxel. Brevifoliol is isolated from the sustainable source and can be semi-synthesised in the laboratory. The detailed studies of brevifoliol and derivatives can provide replacement of taxol.

Conclusion

Taxol is one of the best anticancer drugs till date (Slichenmyer, WJ & Von Hoff DD. 1991) [20] but still has many side effects [21]. Brevifoliol shows almost similar or better anticancer activity at *in-vitro* and its isolation is from non-fatal source and has better aqueous solubility than taxol but still, further investigation is going on. The further research on brevifoliol may lead to the replacement of taxol which has many side-effects.

Conflict of interest

Author has no conflict of interest.

Acknowledgement

The authors would like to acknowledge University of Tabuk for the financial support under research project number **0151-1438-S**.

References

[1] Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant antitumor agents. VI. Isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. Journal of the American Chemical Society. 1971;93(9):2325–2327.

[2] Oberlies NH, Kroll DJ. Camptothecin and taxol: historic achievements in natural products research. Journal of natural products. 2004;67(2):129–135.

[3] Schiff P, Horwitz SB. Taxol stabilizes microtubules in mouse fibroblast cells. Proceedings of the National Academy of Sciences. 1980;77(3):1561–1565.

[4] Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by taxol. Nature. 1979;277(5698):665.

[5] Ramalingam S, Belani CP. Paclitaxel for non-small cell lung cancer. Expert opinion on pharmacotherapy. 2004;5(8):1771–1780.

[6] Baloglu E, Kingston DG. The taxane diterpenoids. Journal of natural products. 1999;62(10):1448–1472.

[7] Shi QW, Zhao YM, Si XT, Li ZP, Yamada T, Kiyota H. 1-Deoxypaclitaxel and a beo-Taxoids from the Seeds of Taxus m airei. Journal of natural products. 2006;69(2):280–283.

[8] Chordia MD, Kingston DG, Hamel E, Lin CM, Long BH, Fairchild CA, et al. Synthesis and biological activity of A-nor-paclitaxel analogues. Bioorganic & medicinal chemistry. 1997;5(5):941–947.

[9] Balza F, Tachibana S, Barrios H, Towers GN. Brevifoliol, a taxane from Taxus brevifolia. Phytochemistry. 1991;30(5):1613–1614.

[10] Khanuja SPS. Santha Kumar TR, Garg A, Misra MK, Chattopadhyay SK, Srivastva S, Negi. vol. 20040127561. AK: United States Patent Publication No; 2002.

[11] Chattopadhyay SK, Tripathi S, Darokar MP, Faridi U, Sisodia B, Negi S, et al. Syntheses and cytotoxicities of the analogues of the taxoid brevifoliol. European journal of medicinal chemistry. 2008;43(7):1499–1505.

[12] Appendino G, Barboni L, Gariboldi P, Bombardelli E, Gabetta B, Viterbo D. Revised structure of brevifoliol and some baccatin VI derivatives. Journal of the Chemical Society, Chemical Communications. 1993;(20):1587–1589.

[13] Georg GI, Cheruvallath ZS, Velde DV, Ye QM, Mitscher LA, Himes RH. Semisynthesis and biological evaluation of brevifoliol 13-[N-benzoyl-(-2′ R, 3′ S)-3′-phenylisoserinate]. Bioorganic & Medicinal Chemistry Letters. 1993;3(6):1349–1350.

[14] Georg GI, Gollapudi SR, Grunewald GL, Gunn CW, Himes RH, Rao BK, et al. A reinvestigation of the taxol content of himalayan taxus wallichiana zucc. and a revision of the structure of brevifoliol. Bioorganic & Medicinal Chemistry Letters. 1993;3(6):1345–1348.

[15] Chu A, Furlan M, Davin LB, Zajicek J, Towers GN, Soucy-Breau CM, et al. Phenylbutanoid and taxane-like metabolites from needles of Taxus brevifolia. Phytochemistry. 1994;36(4):975–985.

[16] Kaur R, Chattopadhyay SK, Chatterjee A, Prakash O, Khan F, Suri N, et al. Synthesis and in vitro anticancer activity of brevifoliol derivatives substantiated by in silico approach. Medicinal Chemistry Research. 2014;23(9):4138–4148.

[17] Kelland LR, Abel G. Comparative in vitro cytotoxicity of taxol and Taxotere against cisplatin-sensitive and-resistant human ovarian carcinoma cell lines. Cancer chemotherapy and pharmacology. 1992;30(6):444–450.

[18] Tremblay S, Soucy C, Towers N, Gunning PJ, Breau L. Characterization of an a beo-Taxane: Brevifoliol and Derivatives. Journal of natural products. 2004;67(5):838–845.

[19] Zhao Y, Guo N, Lou LG, Cong YW, Peng LY, Zhao QS. Synthesis, cytotoxic activity, and SAR analysis of the derivatives of taxchinin A and brevifoliol. Bioorganic & medicinal chemistry. 2008;16(9):4860–4871.

[20] Slichenmyer WJ, Von DH. Taxol: a new and effective anticancer drug.; 1991.

[21] Walker FE. Paclitaxel (TAXOL®): side effects and patient education issues. In: Seminars in oncology nursing. vol. 9; 1993. p. 6–10.