Journal of Medicinal Plants Biotechnology

JMPB

Original Article

A review of the importance of Taxol production from yew (*Taxus baccata* L.)

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ARTICLEINFO

Article history

Submitted: 2020-08-26
Revised: 2020-10-14
Accepted: 2020-11-08

KEYWORDS

Taxus Baccata,
alkaloid,
Taxol,
Anti Cancer

ABSTRACT

The medicinal value of the yew plant, especially *Taxus baccata*, is due to the presence of Paclitaxel under the brand name Taxol in its needle leaves. Taxol, with its antimicrobial properties, causes the death of proliferating cells by preventing the formation of abnormally dividing spindles. Abnormal division stops DNA transcription in the G2 / M division of mitosis and thus causes the proliferation of proliferating cells. Obtained for the first time from the yew plant. The yew tree with the scientific name of *Taxus baccata* L. is one of the coniferous trees of the plant belonging to the Taxaceae family. The yew forests are among the oldest forests in the world and are the heritage of the late third geological period. The yew is an endangered and regenerative plant. And it grows naturally very little. This tree is shade-loving and is distributed in humid and semi-humid areas and its distribution is in the forests of northern Iran. The use of this plant is the treatment of cancer, especially breast, uterine and ovarian cancers, which is related to the composition of taxol. It is a type of alkaloid diterpene that is one of the most effective chemotherapeutic drugs and is on the list of essential drugs of the World Health Organization. This substance is extracted from the skin, roots and other parts of the plant and is still extracted. Valuable plant source has retained its importance and status. Production of taxol through biotechnologies is one of the main options used and has advantages such as independence of production from geographical and environmental conditions, higher production speed and ease of extraction and prevention of extinction of native resources with a positive approach to increase the effective material.

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Introduction

Taxus baccata is a species of evergreen tree in the conifer family and family Taxaceae and genus *Taxus*. There are three species of genus *Taxus* which only *T. baccata* is Iran (Yazdani et al., 2005). *Taxus baccata* is endemic of hyrcanian forests grow from Astara to Aliabad forests in the northern Alborz Mountain with an altitude ranging from 900-1800 m. The original habitat of *Taxus bacata* is Mazandaran and Golestan provinces (Chang et al., 2001). Fussil studies show that yew trees are over 190 million years old and the oldest yew fossils belong to the Miocone and Pliocene periods. In later periods, mixed yew masses with beech and hornbeam species were formed (Mossadegh, 1993). *Taxus baccata* has a long and narrow leaves that is dark green on the upper surface of the leaf and light green on the lower surface. The flowers are exempt from petal and sepal and appear in both male and female forms located on two separate bases (Mossadegh, 1993). *Taxus* species, as low-growing and shade-tolerant dioecious conifer tree, are the source of paclitaxel (Wheeler et al., 1992; Behnam et al., 2016).

Fig. 1. The *Taxus baccata* L. plant

Taxol, generic name paclitaxel, is one of the most successful examples of plant-based anticancer compounds (Liu et al., 2016). Taxol launched by Bristol-myers Squibb. It was first discovered in 1971 from the bark of *Taxus brevifolia* Nutt (Dewick, 2009; Itokawa and Lee, 2002). After pasing the clinical trials in 1980s, FAD approval of paclitaxel application for patients with various tumors, include breast cancer, ovary cancer, AIDS-related Kaposi's sarcoma, lung, blood and needles cancer (Cope, 1998; Jennewein and Croteau, 2001; Phisalaphong and Linden, 1999; Odgen, 1988; Ketchum et al., 2007). Despite the increasing demand for paclitaxel, producing of adequate supplies of the drug became an important issue. During the 1990s, many yew trees were cut down whit the aim of obtaining paclitaxel for medicinal use. Therefore, it is necessary to introduce alterenative source for paclitaxel, several studies conducted among different species-dependent (Croom, 1995). In terms, paclitaxel concentration in the bark and roots were found to be higher than in the wood, needles and branches (Kikuchi and Yatagai, 2003). In an attempt, a semi-synthetic commercial production of paclitaxel with using 10-deacetylbaccatin III from the needles of *T. wallichiana* was developed. However, this method encountered a problem, namely the supply of 10-deacetylbaccatin III from natural yew tree for intermediate of paclitaxel production. Although the chemical synthesis of paclitaxel has been achieved (Holton et al., 1994; Nicolaou et al., 1994). This method is not practical for the mass production of paclitaxel and related taxanes for reasons of cost. Approximately one kilogram of paclitaxel needs processing 10000 kg of bark. Therefore, estimated need of paclitaxel per year is about 250kg of the purified drug, equipollent to a yield from nearly 750000 trees (Wann and Goldner, 1994). Overuse of the yew has exposed it to the risk of extinction (Liao et al., 2006). Accordingly researches were conducted on the production of paclitaxel through another methods such as: tissue culture is another source of paclitaxel and other taxanes. Vegetative propagation of yew can be as a renewable and economic tissue source for increasing paclitaxel production (Tabata, 2006; Mihaljevicet al., 2002; Ho et al., 1998), cell culture is a biotechnological approach for production of paclitaxel and related taxanes in large scales (Fett-Neto et al., 1993;

Wickremesinhe and Arteea., 1993; Onrubia et al., 2013). Callus culture is best starting material for variety of cultures. because we can generate shoots from callus as well as establish suspension cultures (Brunakova et al., 2004), somatic embryogenesis of taxus was also reported (Wann and Goldner., 1994; Jaziri et al., 1996; Manjari and Sumite, 2008; Mahdinejad et al., 2015), micro propagation (Chang et al., 2001), cell suspension culture (Hussain et al., 2011) and taxol-producing endophytic fungi, endophytes are probably pervasive in the plant kingdom, some of which can produce bioactive secondary metabolites similar to or relatively transformed from the metabolites of their host (Jia et al., 2016; Zhou et al., 2010; Nasiri-Madiseh et al., 2010).

Introducing taxol

Taxanes are the main and important compounds of the yew species (Wani et al., 1971; Woods et al., 1996; Miller and Brief, 1980). About 350 taxanes of different yew species have been identified, the most important of which is taxol (Evans, 2002). Taxol is the diterpenoid alkaloid in *Taxus* species (Collin, 2001). That is one of the most effective anticancer drugs and one of the most popular drugs for use in chemotherapy (Expósito et al., 2009).

Taxol Biosynthetic pathway

1: provide of geranyl geranyl diphosphate (GGDP)

2: taxane-ring formation with taxadiene synthase enzyme

3: formation of baccatin III as an important intermediate for taxol biosynthesis

4: esterification of the phenylisoserine side chain of baccatin III

The first step of taxol biosynthesis is the provider of GGDP, that is the universal intermediate of diterpenoid. Taxol is derived from GGDP (Eisenreich et al., 1996). Enzyme 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR), is involved in the first pathway, which is one of the key enzymes in the synthesis of taxol (Zheng et al., 2004).

The second step of taxol biosynthesis is of taxane-ring formation derived from the substrate GGDP and production of taxa-4(5),11(12)-diene by taxadiene synthase (tds) (Wildung et al., 1996; Hezari et al., 1995). Afterward many hydroxylases and the coA-dependent acyltransferases reactions are performed on taxadiene (Jennewein et al., 2004; Schoendorf et al., 2001; Chau and Croteau, 2004; Jennewein et al., 2001; Chau et al., 2004; Walker et al., 2000; Walker and Croteau, 2000), which creates diversity in taxans (Croteau et al., 2006). The hydroxylase enzyme that catalyzed these reactions is a typed of cytochrome P450 hydroxylases of CYP725 family (Mihaliak et al., 1993).

The third step of taxol biosynthesis is formation of baccatin III from taxa-4(5),11(12)-diene, which is done by acetylation in position C10 by 10-deacetyl-baccatin III-10-o-acetyltransferase (DBAT) (Walker and Croteau, 2000). The fourth step of taxol biosynthesis is connection of the side chain at the C13 position of baccatin III. This side chain is α-phenylalanine, that is converted to β-phenylalanine by the phenylalanine aminomutase enzyme (Walker et al., 2004). In the following coA attached to β-phenylalanine by β-phenylalanoyl-coAligase enzyme (Onrubia et al., 2013). The phenylisoserine side chain attached to baccatin III by phenylpropanoid side chain coAacyltransferase(BAPT) (Walker et al., 2002). Finally, the last reaction is performed by N-benzoylation and taxol is synthesized (Walker et al., 2002).

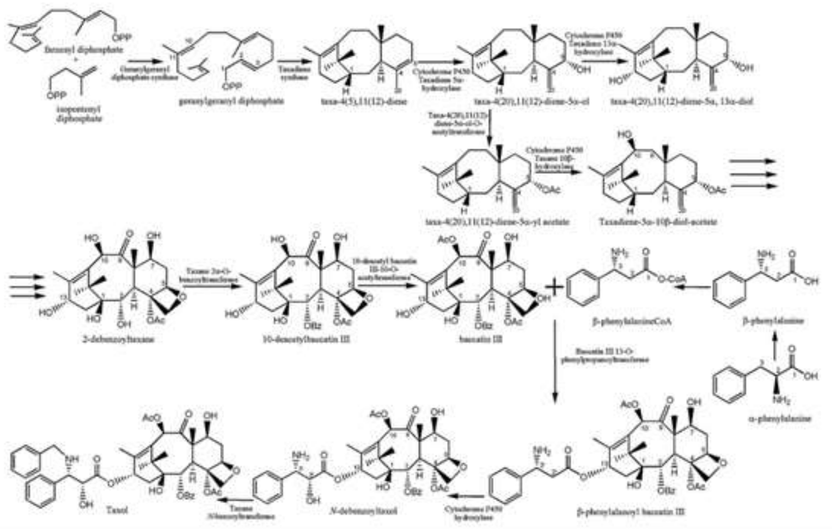

Fig. 2. The biosynthesis pathway of taxol.

Sponsor: This research has not received any financial support from funding organizations.
Conflict of interest: According to the author's statement, this article has no conflict of interest.
Derived from thesis/dissertation: This article is not derived from thesis/dissertation.

References

- Benham, S.E.; Houston Durrant, T.; Caudullo, G.; de Rigo, D. Taxus baccata in Europe: Distribution, habitat,usage and threats. In European Atlas of Forest Tree Species; San-Miguel-Ayanz, J., de Rigo, D., Caudullo, G.,Houston Durrant, T., Mauri, A., Eds.; Publications Office of the EU: Luxembourg, 2016; p. e015921+.

- black pepper (Piper nig rum L.) in Pakistan. Pak. J. Bot., 43 (2):1069-1078.

- Brunakova, K., Babincovaz, Z., Takac, M. and Cellarova, E. (2004). Selection of callus cultures of Taxus baccata L. as a potential source of paclitaxel production. Engineering in Life sciences, 4, 465–469.

- Chang SH, Ho CK, Chen ZZ, Tsay JY. Micropropagation of Taxus maireifrom mature trees. Plant Cell Rep 2001; 20(6):496-502.

- Chang, S.H., Ho, C.K., Chen, Z.Z., Tsay, J.Y., Micropropagation of Taxus mairei from mature trees. Plant Cell Rep , 2001,Vol. 20, pp. 496-502.

- Chau, M., Croteau, R. Molecular cloning and characterization of a cytochrome P450 taxoid 2alpha-hydroxylase involved in Taxol biosynthesis. Arch. Biochem. Biophys.2004, 427, 48–57.

- Chau, M., Jennewein, S., Walker, K., Croteau, R. Taxol biosynthesis: Molecular cloning and characterization of a cytochrome P450 taxoid

7betahydroxylase. Chem. Biol.2004, 11, 663–672.

- Collin, H. A. (2001). Secondary product formation in plant tissue cultures. Plant Growth Regulation, 34, 119-134.

- Cope, E.A. Taxaceae: The genera and cultivated species. Bot. Rev. 1998, 64, 291–322.

- Croom, E.M., Jr. Taxus for taxol and taxoids. In: Suffness, M. (Ed.), TAXOL science and applications. CRC Press, NewYork, 1995, pp. 37–70.

- Croteau R, Ketchum REB, Long RM, Kaspera R and Wildung M. Taxol biosynthesis and molecular genetics. Phytochemistry Reviews 2006; 5: 75-97.

- derivatives. Journal of Natural Products 43: 425-437.

- Dewick, P.M., Medicinal natural products: a biosynthetic approach. (3rd Ed.). John Wiley & Sons Ltd., 2009.

- Eisenreich, W., Menhard, B., Hylands, P.J., Zenk, M.H., Bacher, A. Studies on the biosynthesis of taxol: the taxane carbon skeleton is not of mevalonoid origin. Proc. Natl. Acad. Sci. USA1996, 93, 6431–6436.

- Evans, W. C. (2002) Trease and evans pharmacognosy. W. B. Saunders, Edinburgh, London, New York.

- Expósito, O., Bonfill, M., Moyano, E., Onrubia, M., Mirjalili, M., Cusido, R. and Palazon, J. (2009) (2009) Biotechnological production of taxol and related taxoids: current state and prospects. Anticancer Agents in

Medicinal Chemistry- Anti Cancer Agents 9(1): 109-121.

- Fett-Neto AG, Melanson SJ, Sakata K, DiCosmo F. Improved growth and taxol yield in developing calli ofTaxus cuspidataby medium composition modification. Nat Biotechnol. 1993;11(6): 731–4.

- Hezari M, Lewis NG and Croteau R. Purification and characterization of taxa-4(5),11(12)-diene synthase from pacific yew (Taxus brevifolia) that catalyzes the first committed step of taxol biosynthesis. Archives of Biochemistry and Biophysics1995; 322: 437-444.

- Ho CK, Chang SH, Tasi JY. 1998. Selection breeding, propagation, and cultivation of Taxus mairei in Taiwan (in Chinese with English summary). Handb Taiwan For Res Inst. 88, 65-82.

- Holton, R.A., Somoza, C., Kim, H.-B., Liang, F., Biediger, R.J., Boatman, P.D. First total synthesis of taxol.J. Am. Chem. Soc.1994, 116, 1597–1599.

- Hussain, A.; Naz, S.; Nazir, H. and Shinwari, Z.K. (2011).Tissue culture of

- Itokawa H. and Lee K-H. Taxusthe genus Taxus. Taylor and Francis. 2002. London and new york.

- Jaziri, M., A. Zhiri, Y.W. Guo, J.P. Dupont and K. shimomora, 1996. Taxus sp. Cell, tissue and organ cultures as alternative sources for taxoid production: A literature survey. Plant Cell Tissue Organ cult., 46:59-75.

- Jennewein, S., Croteau, R., Taxol: biosynthesis, molecular genetics and biotechnological applications. Appl Microbiol Biot , 2001, vol. 57, pp. 13-19.
- Jennewein, S., Long, R.M., Williams, R.M., Croteau, R. Cytochrome p450 taxadiene 5alpha-hydroxylase, a mechanistically unusual monooxygenase catalyzing the first oxygenation step of taxol biosynthesis. Chem. Biol.2004, 11, 379–387.
- Jennewein, S., Rithner, C.D., Williams, R.M., Croteau, R.B. Taxol biosynthesis:
- Jia, M., Chen, L., Xin, H.-L., Zheng, C.-J., Rahman, K., Han, T., & Qin, L.-P. (2016). A friendly relationship between endophytic fungi and medicinal plants: A systematic review. Frontiers in Microbiology, 7, 906.
- Ketchum REB, Horiguchi T, Qiu D, Williams RM, Croteau RB (2007). Feeding cultured Taxus cells with early precursors reveals bifurcations in the taxoid biosynthetic pathway. Phytochemistry 68: 335-341.
- Kikuchi, Y., Yatagai, M. The commercial cultivation of Taxusspecies and production of taxoids. In: Itokawa, H., Lee, K.-H. (Eds.), Taxus: The genus Taxus. Taylor & Francis, London, 2003, pp. 151–178.
- Liao, Z., M. Chen, X. Sun and K. Tang, 2006. Micropropagation of endangered plant species.

Methods Mol. Biol., 318:179-185.

- Liu WC, Gong T and Zhu P. Advances in exploring alternative Taxol sources. Royal Society of Chemistry Advances2016; 6: 48800-48809.

- Mahdinejad, N.; Fakheri, B.A. and Ghanbari, S. (2015). Effects of growth regulators on in vitro callogenesis of Taxus baccata L. biological forum-An International Journal, 7(1):142-145.

- Manjari, D.M. and J. Sumite, 2008 . Plant regeneration through somatic embryogenesis in Taxus wallichiana. J. Plant Biochem. Biotechnol., 17:37-44.

- Mihaliak CA, Karp F and Croteau R. Cytochrome P-450 terpene hydroxylases in Lea PJ. ed. Methods plant biochem. Enzymes of secondary metabolism. Academic press, London. 1993; 9: 261-279.

- Mihaljevic S, Bjedov I, Kovac M, Levanic DL, Jelaska S. 2002. Effect of explants source and growth Regulators on in vitro callus growth of Taxus baccata L. Washingtonii. Food Tech Bio. 40(4), 299-303. UDC 57.086.83.006.2:582.85. ISSN 1330-9862.

- Miller, R. W. and Brief, A. (1980) Survy of taxus alkaloids and other taxane

- Mossadegh, A. (1993) Yew tree. Research Report of University of California, Berkeley.

- Nasiri-Madiseh Z, Mofid MR, Ebrahimi M, Khayyam-Nekoei SM, Khosro-Shahli M.

Isolation of Taxol-producing endophytes fungi from Iranian yew (Taxus baccataL.). J Shahrekord Univ Med Sci 2010; 11(4): 101-7. [in Persian]

- Nicolaou, K.C., Yang, Z., Liu, J.J., Ueno, H., Nantermet, P.G., Guy, R.K. Total synthesis of taxol. Nature 1994, 367, 630–634.

- Odgen L (1988) Taxus (yews)- a highly toxic plant. Vet. Hum. Toxicol. 30: 653-564.

- Onrubia M, Cusido RM, Ramirez K, Hernandez-Vazquez L, Moyano E, Bonfill M and Palazon J. Bioprocessing of plant in vitrosystems for the mass production of pharmaceutically important metabolites: Paclitaxel and its derivatives. Current Medicinal Chem. 2013; 20: 880-891.

- Onrubia., Moyano E, Bonfill M, Cusido RM, Goossens A, Palazon J. Coronatine, a more powerful elicitor for inducing taxane biosynthesis in Taxus mediacell cultures than methyl jasmonate. J Plant Physiol. 2013;170(2):211–9.

- Phisalaphong, M.A., Linden, J.C., Kinetic studies of paclitaxel production by Taxus canadensis cultures in batch and semicontinuous with total cell recycle. Biotechnol Progr , 1999, Vol. 15, pp. 1072–1077.

- Schoendorf, A., Rithner, C.D., Williams, R.M., Croteau, R.B. Molecular cloning of a cytochrome P450 taxane 10betahydroxylase cDNA from Taxusand functional expression in yeast. Proc. Natl.

Acad. Sci. USA2001, 98, 1501–1506.

- Tabata H. Production of paclitaxel and the related taxanes by cell suspension cultures of Taxusspecies. Current Drug Targets 2006; 7(4):453-61.

- taxane 13alpha-hydroxylase is a cytochrome P450-dependent monooxygenase. Proc. Natl. Acad. Sci. USA 2001, 98, 13595–13600.

- taxinine and its derivatives. Tetrahedron 22: 243-260.

- Walker K, Klettke K, Akiyama T and Croteau RB. Cloning, heterologous expression, and characterization of a phenylalanine aminomutase involved in taxol biosynthesis. Journal of Biological Chem. 2004; 279: 53947-54.

- Walker K, Long R and Croteau R. The final acylation step in Taxol biosynthesis: cloning of the taxoid C13-side-chain N-benzoyltransferase from Taxus. Proceedings of the National Academy of Sciences USA 2002; 99: 9166-71.

- Walker K; Fujisaki S; Long R and Croteau R. Molecular cloning and heterologous expression of the C-13 phenylpropanoid side chain-CoA acyltransferase that functions in taxol biosynthesis. Proceedings of the National Academy of Sciences USA 2002; 99 (20): 12715-12720.

- Walker, K., Croteau, R. Molecular cloning of a 10-deacetylbaccatin III-10-O-acetyl transferase cDNA from Taxusand functional expression in Escherichia coli.

Proc. Natl. Acad. Sci. USA2000, 97, 583–587.

- Walker, K., Croteau, R. Taxol biosynthesis: molecular cloning of a benzoylCoA:taxane 2alpha-O-benzoyltransferase cDNA from Taxusand functional expression in Escherichia coli. Proc. Natl. Acad. Sci. USA 2000, 97, 13 591–13 596.

- Walker, K., Schoendorf, A., Croteau, R. Molecular cloning of a taxa-4(20),11(12)-dien-5alpha-ol-O-acetyl transferase cDNA from Taxusand functional expression in Escherichia coli. Arch. Biochem. Biophys. 2000, 374, 371–380.

- Wani, M. C., Taylor, H. L., Wall, M. E., Coggon, P. and McPhail, A. T. (1971) Plant antitumor agents. VI. Isolation and structure of taxo. a novel antileukemic and antitumor agent from Taxus brevifolia. Journal of the American Chemical Society 93(9): 2325-2327.

- Wann,S.R. and W.R. Goldner, 1994. Induction of somatic embryogenesis in Taxus and the production of taxan-ring alkaloids thereform. United states Pateant 5310672.

- Wheeler, N.C.; Jech, K.; Masters, S.; Brobst, S.W.; Alvarado, A.B.; Hoover, A.J.; Snader, K.M. Effects of genetic,epigenetic, and environmental factors on taxol content in Taxus brevifolia and related species. J. Nat. Prod.1992, 55, 432–440.

- Wickremesinhe ER, Arteea RN.Taxuscallus cultures: initiation, growth optimization, characterization and taxol production. Plant Cell Tissue Organ Cult. 1993;35(2):18193.

- Wildung, M.R., Croteau, R. A cDNA clone for taxadiene synthase, the diterpene cyclase that catalyzes the committed step of taxol biosynthesis. J. Biol. Chem.1996, 271, 9201–9204.

- Woods, M. C., Nakanishi, K. and Bhacca, N. S. (1996) The NMR Spectra of

- Yazdani D., Shahnazi S., Rezazadeh S. and Pir Ali Hamedani M. (2005). A review on T. baccata. J Med Plants 4(15): 1-8.

- Zheng, Q.P., Yu, L.J., Liu, Z., Li, M.Y., Xiang, F., Yang, Q. Cloning and analysis of cDNA encoding key enzyme gene (dxr) of the non-MVA pathway in Taxus chinensiscells. Sheng Wu Gong Cheng Xue Bao 2004, 20, 548–553 (in Chinese).

- Zhou X, Zhu H, Liu L, Lin J, Tang K. A review: recent advances and future prospects of taxol-producing endophytic fungi. Appl Microbiol Biotechnol 2010; 86(6): 1707-17.