Journal of Medicinal Plants Biotechnology

Vol 7, No 1, Spring & Summer 2021

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

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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.

Keywords: *Taxus Baccata*, alkaloid, Taxol, Anti Cancer

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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).

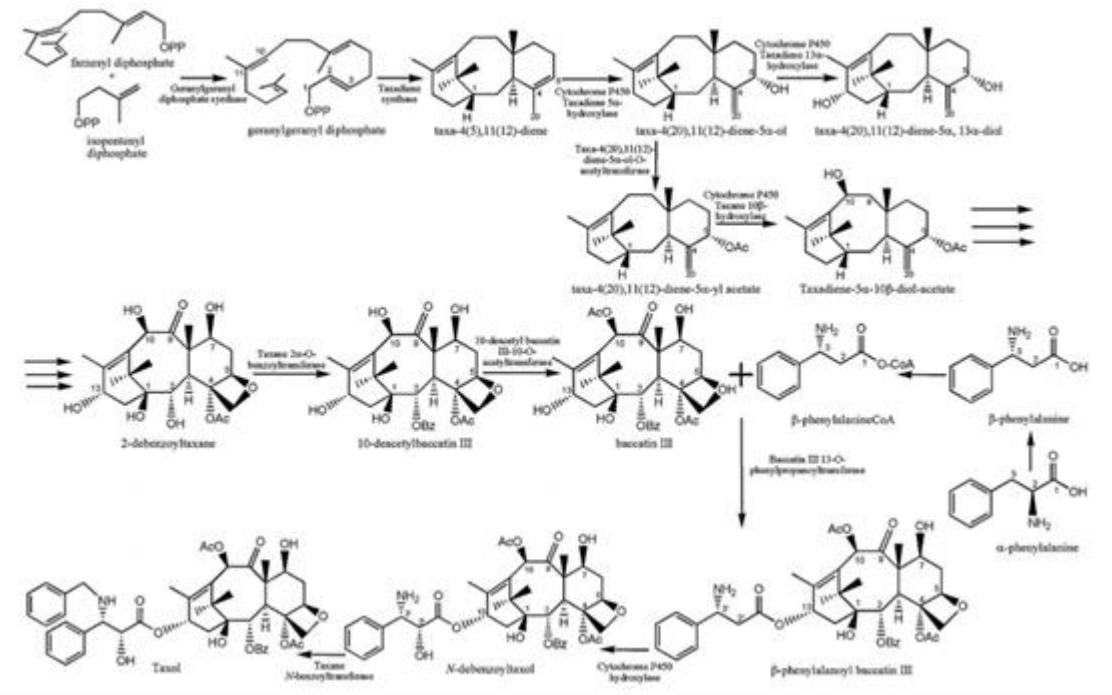

Fig. 2. The biosynthesis pathway of taxol.

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