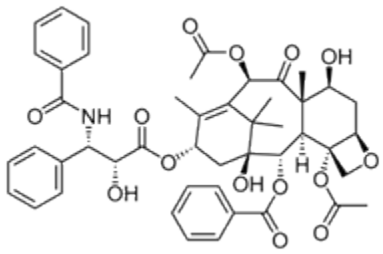
TAXANES

Overview



The taxanes are a family of chemotherapeutic agents derived from certain species of yews (coniferous trees of the genus *Taxus*). Paclitaxel, nicknamed*taxol* by the original researchers (and later marketed under the trade name Taxol), was the first of the taxanes to be developed, and is perhaps the most well-known and controversial chemotherapy drug in existence. The compound was first isolated from Pacific yew bark in the 1960s, under a program organized by the U.S. National Cancer Institutes and the U.S. Department of Agriculture to systematically screen plant compounds for their anti-cancer potential (Goodman and Walsh 2001, p. 9). Among cancer chemotherapies, taxanes are routinely used in the treatment of a wide range of cancers, including ovarian, breast, non-small cell lung, head and neck, stomach, prostate, and testicular cancers, as well as leukemia. Research is underway to expand use of the drug beyond the cancer setting (Liggins et al 2004; Kurose et al 2001).

Paclitaxel is a naturally occurring substance in the bark of the slow-growing Pacific yew tree (*Taxus brevifolia*), and it is the nature of this source that generated a firestorm of controversy soon after the drug was licensed for development. Paclitaxel was welcomed by oncologists, particularly for its effects against cancers that fail to respond to other powerful anti-cancer agents, including anthracyclines. Among environmentalists, however, the drug was simultaneously a poster child for biodiversity and a major threat

to the dwindling old growth forests of the U.S. Pacific coast, the habitat of the Pacific yew (Goodman and Walsh 2001, p. 77).

By the original production process, it took twelve kilos (over 24 pounds) of Pacific yew *bark* to produce a mere *half*gram of taxol (Goodman and Walsh 2001, p.56). At that production rate, more yew bark than the forests could supply would be required in order to meet even a decade's demands, threatening destruction of the Pacific yew and the ecosystem to which it belonged (Goodman and Walsh 2001, p. 102-103). That ecosystem was home to, among other endangered species, the spotted owl (*Strix occidentalis)*, which was already the mascot for the battle between environmentalists and the logging industry.[1] Even vice presidential candidate Al Gore weighed in on the taxol controversy in his book on environmental sustainability, *Earth in the Balance* (Gore 1992, p. 119).

Much of this debate took place in a policy vacuum since, prior to the discovery of taxol, little was known about the Pacific yew and the Forest Service had not yet adjusted its management philosophy from resource development to balanced preservation. When taxol was under initial development, the Forest Service considered yews commercially valueless, and granted permits to harvest the trees for fence posts at the cost of twenty five cents per tree (Goodman and Walsh 2001, p.83). The timing could not have been worse: a lifesaving drug that required very large quantities of bark, from a poorly understood tree in a threatened environment, at a time when the Forest Service policy was ill equipped to handle resource conflicts.

The National Cancer Institutes-Department of Agriculture alliance under which taxol was originally explored dissolved before the drug entered development. Facing the difficult logistical problems of securing adequate yew bark, the National Cancer Institutes instead granted what would become a highly controversial exclusive marketing license to Bristol-Myers Squibb (BMS) (Goodman and Walsh 2001, p.2). The license gave BMS an effective monopoly, allowing them to price taxol as they pleased, though they had borne none of the cost or risk of the initial drug discovery and proving process. And, though the original exclusive production license granted in 1991 had a term of five years, BMS filed for and received multiple patents relating to the drug and, on the strength of these questionable patents, fought even after 1998 to keep generics off the market. (E.g., *The Scientist*, 2003). These suits ultimately failed, though the tangled issues of control of the taxol market persisted.

In the end, pressures resulting from the costly and politically sensitive supply led researchers in the United States and Europe to find less destructive means of producing the drug. The first major step forward came when French researchers determined that constituent chemicals much more plentiful than paclitaxel itself were actually responsible for the anti-tumor effects (Goodman and Walsh 2001). This promised to lessen some of the logistical and political pressure around sourcing, and suggested new avenues for synthesizing the drug in a laboratory. Eventually, and as part of its commitment under the licensing agreement, BMS modified its production methods to use cultivated trees, and it now manufactures the compound from cultured cells. The compound has also been found to be produced by certain fungi, which may provide additional sources of cultured production (Stierle and Strobel, et al. 1993).

In addition to paclitaxel, a related taxane, docetaxel (marketed under the trade name Taxotere), has been derived from the European yew (*Taxus baccata*). The European yew is not only more plentiful in the wild, but is actively cultivated as a landscape plant; this availability relieves docetaxel, for the most part, from the environmental and political pressures that greeted paclitaxel.

Paclitaxel is among the most widely consumed chemotherapy drugs, with the world market for the now generically available compound at $195 million in 2007 (Global Industry Analysts 2008). This represents a decrease from the more than $1.3 billion in annual sales that BMS enjoyed as the sole producer, and under noncompetitive pricing, through the late 1990s, though production volumes have continued to increase (Goodman and Walsh 2001, p. 2).

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