Hot Topics in Pharmacognosy: Fungal Taxol and Its Role(s) in the Yew Tree

By Dr. David J. Newman

As has become obvious over the last few years, there have been some very interesting papers demonstrating that there are fungal endophytes in a variety of plants that when isolated and then fermented outside of the plant, and in some cases, when supplemented in those fermentations with either plant or microbial extracts, increased yields have been seen. However, until very recently, these were considered by a large number of botanists and some natural product chemists, as being artifacts and not related in any way to production of taxol by fungal genes. Comments such as "carry-over," "no complete genomic characterizations," etc., were made both in press and verbally at meetings when these possibilities were discussed and/or presented.

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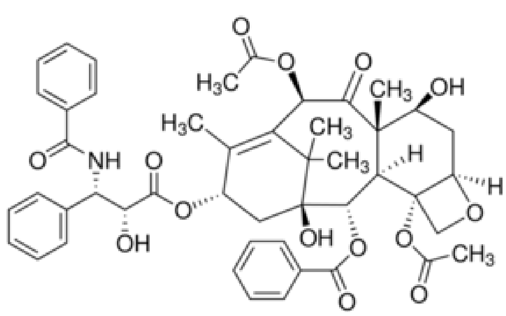
A recent paper in *Current Biology* by Soliman et al..[1] has now thrown open an entirely new possibility that covers the production of fungal taxol in the yew with experimental evidence of its role as a protective agent. From the early days of studying fungal tubulin, though at the time the actual protein was not identified, it was subsequently realized that antitubulin agents were excellent antifungal agents as first demonstrated by Hastie in 1970 with benomyl[2] and then further developed in later papers from Hastie's group in 1976[3] and with more details given in a 1986 publication in *Annual Reviews of Phytopathology* in 1986.[4] Obviously in the intervening period the results of Horwitz's studies were published in *Nature* in 1979[5] showing the mechanism of action of the cytotoxin taxol, first reported by Wani et al. in 1971.[6]

Taxus brevifolia

However, the paper by Soliman now opens up the topic of fungal production of taxol as a protective mechanism for the tree when attacked by wood rotting fungi. Not being a botanist, I will have to accept at face value the report in this paper that in the branch growth of *Taxus*, cracks occur in the protective bark layer that allow in pathogenic fungi (wood rotting fungi for example). In an excellent series of clever experiments, Soliman and colleagues demonstrated that the endophyte *Paraconiothyrium* strain SSM001 present in the tree migrated to the "cracks" and other pathogen entry points and effectively laid down an antifungal carpet of taxol. The fungal taxol was produced by the fungus and then sequestered within the fungus in intracellular hydrophobic bodies. When the presence of an invader was "sensed" (which had to be a chemical signal analogous to a quorum sensing agent, think pheromone in human terms), the hydrophobic bodies were release via exocytosis, laying down the "antifungal carpet."

In a further series of elegant experiments, Soliman et al. demonstrated that fungal taxol did not interfere with the plant's own metabolism if in the hydrophobic bodies, whereas in their absence, taxol inhibited plant cell growth as would be expected. In addition, the endophyte was insensitive to taxol. This brings up the interesting point that taxol, when isolated from the yew tree, is found generally in the outer stem wood and particularly in the bark. If one thinks about this from a hydrodynamic perspective, taxol may be sequestered in areas of the tree where it will not get back into areas of growth. Its presence in the leaves may well be due to the presence of taxol-producing endophytes in these organs.

What was also of significant interest was a series of experiments reported in the paper that demonstrated that supplementation of the endophyte's ex-planta fermentation with chitin or in particular, methyl chloride (chloromethane), a known fungal metabolite of wood decaying fungi from metabolism of lignin, induced a significant increase in production of taxol in the fermentation.



Taxol

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Soon after the paper referred to above was published, Zhang et al.[7] published a very interesting paper on a genetic analysis of the micro-

continued on page 14

continued from page 13

bial consortium found in the roots of *Taxus chinenis* where they showed 187 operational taxonomic units including fungi with the necessary genes to produce taxol if the methodologies to induce expression were available. They allude to genetic evidence that the gene clusters in microbes for taxol production might differ from the plant, which is similar to the report by Yang et al.[8] that reported that the genes involved in taxol production by the endophyte *Penicillium aurantiogriseum* NRRL 62431 differed from those in the plant. Further discussion of the role of microbes in taxol production can be seen in the 2014 review by Gond et al.[9] and also discussed by Newman and Cragg in 2015 in a *Frontiers in Chemistry* article.[10]

Thus the various role(s) of taxol in the plant and the microbe may differ or may simply be successive operations in the protection of the plant from predation by fungi. It would be interesting to see a report of the microbial content of the callus cultures used in the plant cell culture production of taxol on an industrial scale, but so far nothing has been reported on this topic as far as can be determined. ■

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