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Endophytes as alternative paclitaxel sources

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Chapter 1

Introduction & scope of the thesis

Pharmaceutical Biology perceives plants as 'bio-factories' of potentially valuable therapeutic compounds. Even now, in the era of modern chemistry, technology and automation, it is impossible to underestimate the impact of plant-derived natural products as pharmaceutically relevant lead compounds. In fact, world's most universally used drug Aspirin™ is a derivative of salicylic acid originally obtained from white willow (*Salix alba*).

Plants, like all other organisms, live immersed in a thriving community of microbes. The diversity of fungi, oomycetes and bacteria with which plants co-exist can bring both plague and benefit. However, parasitic and symbiotic associations are merely the two extreme outcomes of a continuum of interorganismal interactions. Remarkably little is understood about plant--microbe interplay that is, at first glance, symptomless. Complex communities of poorly studied plant-associated microbes, endophytes could prove to be a yet untapped reservoir of natural products bearing pharmaceutical potential. The more we understand how plants tame, thwart and succumb to their 'bugs' and *vice versa*, the more likely we will be able to extract new resources for potentially novel and successful disease treatments.

The following section of the hereby presented thesis (**chapter 2**) gives an extensive overview of the current state of knowledge about endophytes. Starting with the disambiguation of the very definition of endophytic organisms, it gives account of their impact on pharmaceutical, as well as agricultural arenas. Further, it focuses on the nature of the interactions between endophytes and their plant hosts, taking heed of the importance of evolutionary genetics and ecological factors. Moreover, the genetic background of endophytic biosynthetic pathways is discussed with an emphasis put on recent advances in functional genomics as a driving force for a better understanding of endophytic microbes and for their further exploiting as a source of therapeutically relevant compounds presumed to push forward the frontiers of drug discovery.

Paclitaxel, the world's first billion dollar anticancer medication, was originally derived from the inner bark of Pacific yew (*Taxus brevifolia*). While an array of reports on alternative, endophytic paclitaxel producers seemed to have caused quite a controversy over the past two decades, we carried out an in-depth investigation of *Taxomyces andreanae* – the very first

presumed endophytic synthesizer of the valuable antineoplastic diterpenoid (**chapter 3**).

The greatest botanical surprise of the last century, *Wollemia nobilis* is not only one of the oldest plant species on the globe, but was also reported to host a paclitaxel producing endophyte, *Pestalotiopsis guepinii*. Consecutive sections of the thesis deal with the *in vitro* culturing (**chapter 4**), chemistry (**chapter 5**) and endophytic flora (**chapter 6**) of the unique conifer.

Finally, **chapter 7** integrates the results of the studies described in the thesis and presents future perspectives.