Thieme

# Paclitaxel – a Product of Fungal Secondary Metabolism or an Artefact?#



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## ABSTRACT

Taxol (common name: paclitaxel) is an extremely important component of drugs for the treatment of various cancers. Thirty years after the discovery of its effectiveness, a metabolic precursor of Taxol (10-deacetylbaccatin III) is still primarily extracted from needles of European yew trees. In order to meet the considerable demand, hopes were pinned on the possibilities of biotechnological production from the very beginning. In 1993, as if by chance, Taxol was supposedly discovered in fungi that grow endobiotically in yew trees. This finding aroused hopes of biotechnological use to produce fungal Taxol in large quantities in fermenters. It never came to that. Instead, a confusing flood of publications emerged that claimed to have detected Taxol in more and more eukaryotic and even prokaryotic species. However, researchers never reproduced these rather puzzling results, and they could certainly not be applied on an industrial scale. This paper will show that some of the misguided approaches were apparently based on a seemingly careless handling of sparse evidence and on at least questionable publications. Apparently, the desired gold rush of commercial exploitation was seductive. Scientific skepticism as an indispensable core of good scientific practice was often neglected, and the peer review process has not exerted its corrective effect. Self-critical reflection and more healthy skepticism could help to reduce the risk of such aberrations in drug development. This article uses this case study as a striking example to show what can be learned from the Taxol case in terms of research ethics and the avoidance of questionable research practices.

## Introduction

Taxol (common name: paclitaxel) is still among the most important drugs in cancer therapy today [1–3]. On the one hand, the detection and application of the active ingredient is one of the great success stories of natural product research [4]. On the other hand, however, some chapters of that story are an example of how science can be misled by a mixture of repeated negligence, a lack of (self-)criticism, presumably a lack of interdisciplinary exchange, a focus on potential commercial applications, and a prevalent research mentality, which was neither sufficiently open-ended nor sensitive to possible sources of error. In particular, the strong hope of obtaining Taxol biotechnologically from fungi has repeatedly failed to fulfil the requirements of good scientific practice [5].

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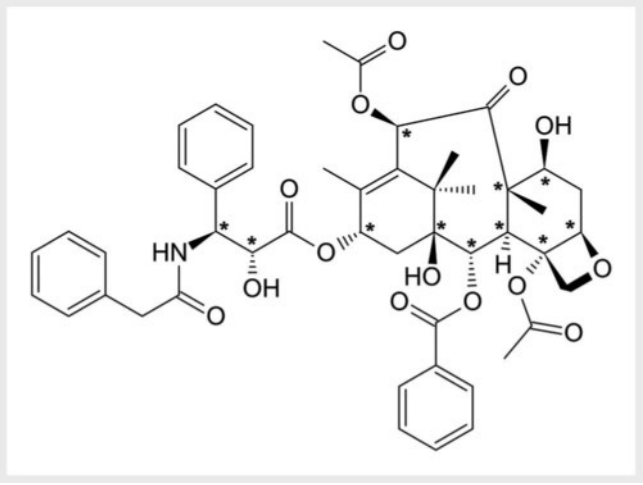
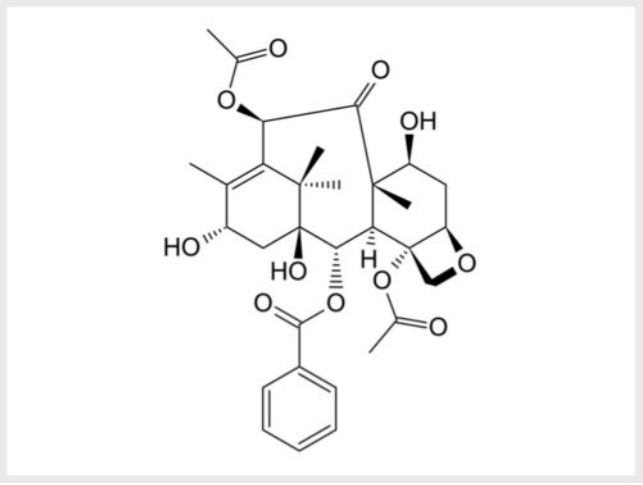


▶ **Fig. 1** Taxol (chiral centers marked).



▶ **Fig. 2** Baccatin III.

## The History of Taxol as a Drug

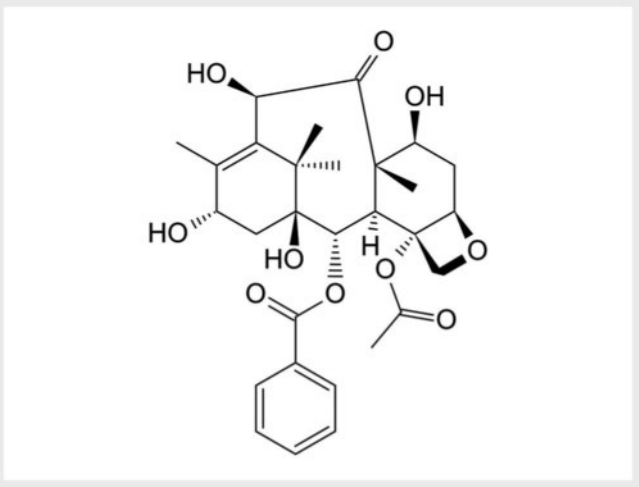
In the early 1970 s, Taxol was identified in the bark of the Pacific yew (*Taxus brevifolia* Nutt., Taxaceae), and its sterically complex structure was elucidated [6]. Taxol binds to tubulin and disrupts the formation of the spindle apparatus, making it a mitosis inhibitor, which is why it is used as an effective pharmacological agent against cell growth in various cancers, in particular, ovarian and breast cancer [1–4, 7–11]. The mechanism of action was decisively clarified in 1979 by a research team led by Susan Band Horwitz [12]. In 1977, the first report on the *in vivo* proof of principle was published, based on animal models [13]. In 1983, the first clinical trials were carried out on humans, which yielded positive results with regard to ovarian cancer in 1988 [14]. Taxol, as a drug, was authorized by the Food and Drug Administration (FDA) in the USA in 1992 [15]. It was clear that the yield from the bark of the Pacific yew, in which the compound is accumulated, was too low to meet the global demand for Taxol. *Taxus brevifolia*, which grows extremely slowly, would have been decimated in just a few years [8, 16, 17]. The supply problem arose right from the start, and approaches were made very early on [18–21] to find possible solutions by obtaining Taxol from cell cultures [18, 22]. When Taxol was authorized, as an immediate legal response, the US Pacific Yew Act 1992 [23] placed the tree under strict rules of sustainable management [24].

A total synthesis of Taxol is extremely difficult due to its steric complexity (with 11 chiral centers, ▶ **Fig. 1**). Although the compound has been successfully synthesized several times since 1994 using different synthesis routes [25–30], it is not possible to produce it on an industrial scale in the laboratory. Eugene H. Cordes, who for many years headed a research department at Merck and later at Sterling Winthrop Pharmaceuticals, took a more practical view and remarked laconically [31]: “There are now seven published syntheses of taxol in the chemical literature. All are triumphs of chemical wit and ingenuity, and none is remotely useful for commercial scale manufacture of taxol”. Today, Taxol is mainly obtained from the needles of the European yew (*Taxus baccata* L., Taxaceae), a renewable resource, by extraction and semi-synthetic processing of the precursors baccatin III (▶ **Fig. 2**) and (in the main) 10-deacetylbaccatin III (▶ **Fig. 3**) [7, 32] or from cell cultures created from meristematic cells of the yew cambium [7–9]. In principle, it seems that there are no longer any fundamental problems in meeting the demand for this proven anti-cancer drug, although this is sometimes assessed differently [33–35]. Reliable data that would allow the assessment of the coverage of demand are not available.

## Highly Conserved Taxol Synthesis in a Colorful Bouquet of Different Species?

However, 30 years ago, when the quantitative production of Taxol was still a major challenge, a pharmaceutical gold rush began that sometimes failed to withstand the mechanisms of critical self-control of responsible research. In 1993, a team of researchers claimed to have discovered an endophytic fungus (baptized *Taxomyces andreanae*, family still unassigned) in the bark of the Pacific yew, which was reported to produce Taxol itself [36, 37]. As a precaution, a patent was applied for immediately. The leading journal *Science* ran the headline: “Surprise! A Fungus Factory For Taxol?” [38]. However, the detection was rather indirect via immunoassay and mass spectrometry, not, for example, by means of NMR spectra on preparatively isolated material. As a result of the publication, an almost unmanageable number of articles appeared over the following 30 years, in which not only was the alleged discovery uncritically adopted, but new organisms constantly emerged that allegedly produce Taxol, including various fungi and even various prokaryotes. The hunt for other species producing Taxol began in the mid-1990 s [39, 40].

An early review article from 2010 already listed an impressive 29 endophytic fungal species that are said to be able to produce Taxol [41]. For example, it was claimed that Taxol was detected in endophytic fungi of the species *Pestalotiopsis versicolor* Speg. and *Pestalotiopsis neglecta* Thüm. (Sporocadaceae) from the Japanese




▶ **Fig. 3** 10-Deacetylbaccatin III.

yew *Taxus cuspidata* Sieb. & Zucc. (Taxaceae) [42]. Another team of researchers claims to have isolated the human pathogenic mold *Aspergillus fumigatus* Fresen. (Aspergillaceae) from samples of yew bark from the Indian state of Himachal Pradesh in the Himalayas, which was also reported to produce Taxol [43]. The article does not even specify the yew species from which the samples were collected. The host species generally remains unidentified as *Taxus sp*. This apparently did not prevent the article from being accepted for publication. New alleged discoveries of Taxol in fungi kept coming up [29, 44–48]. Various research groups assert that Taxol is produced, for example, by another mold, *Aspergillus niger* Tiegh (Aspergillaceae) [44], by the basidiomycete *Grammothele lineata* Berk. & M. A.Curtis (Polyporaceae) isolated from jute mallow, *Corchorus olitorius* L. (Malvaceae) [49], or from the ascomycete *Alternaria brassicicola* Schwein. (Pleosporaceae) isolated from the plant *Terminalia arjuna* Wight & Arn. (Combretaceae) [50]. One of the most remarkable original articles is a publication that claims to have used NMR spectra to detect Taxol in the fungus *Pestalotiopsis hainanensis* A. R. Liu, T. Xu & L. D. Guo (Sporocadaceae) that was found in the dermatitic scurf of the giant panda *Ailuropoda melanoleuca* David (Ursidae) [51]. Anyone who finds Taxol in the scurf of panda bears, of all things, must have been looking for it precisely there. It is not completely clear how the research team came up with this rather innovative but also puzzling lead. While the research team was reasoning their finding with previous isolations of allegedly Taxol-producing *Pestalotiopsis* sp., it remains a mystery how the panda bear's skin did react to presumed fungal Taxol.

A review essay, referring to other references (most of them in turn review essays), mentions a strikingly colorful spectrum of taxonomically quite different plant species: *Polylepis neglecta* M. Kessler (Rosaceae), *Gingko biloba* L. (sole species of the Ordo *Ginkgoales*), *Citrus medica* L. (Rutaceae), *Tarenna asiatica* (L.) Kuntze ex K.Schum. and *Maguireothamnus speciosus* Steyerm. (both Rubiaceae), *Hibiscus rosasinensis* L. (*Malvaceae*), and *Taxodium distichum* (L.) Rich. (Cupressaceae) [8]. The production of Taxol has allegedly been verified, to give another example, in the common hazel *Corylus avellana* L. (Betulaceae) [52, 53] and is even said to be additionally stimulated and significantly increased in a hazel cell culture solution by fungi of the species *Camarosporomyces flavigenus* (Constant. & Aa) Crous (Coniothyriaceae) [54]. Of course, it is not impossible that different dicotyledons are capable of synthesizing the same complex biomolecule. However, this seems to require at least some explanation and would have provoked critical questions from a plant-physiological, ecological, and evolutionary-biological perspectives. The genetic make-up to produce a sterically complex biomolecule such as Taxol is obviously not conserved in evolutionary biology – despite all the suspected findings, it is still a very rare natural substance. But then it seems, at least *prima facie*, rather implausible that the same synthesis pathway (or at least the identical product) would occur by chance in species that are extremely distant in terms of evolutionary biology (such as eukaryotes from the disparate kingdoms of fungi and of plants and prokaryotic bacteria), especially since no common ecological function is recognizable. The synthesis of Taxol requires at least 19 enzyme-catalyzed reactions [8] that lead to a very specific and sterically demanding ring system. The amount of energy required for this alone would be highly improbable in terms of evolutionary biology if it could not fulfill an ecological function. In the case of yews, this may plausibly be the defense against herbivores or infections by eukaryotic microorganisms. But this is not equally plausible for other species, especially as they occupy completely different ecological niches. It is even more implausible why other organisms should extremely selectively produce Taxol, while there is a whole spectrum of consistently toxic alkaloids with a taxine-based structure.

Admittedly, there are still considerable uncertainties about the evolution of metabolic pathways [55]. Some even argue that natural substances of secondary metabolism only very rarely develop specific biological activity at all and that the evolutionary advantage lies in the abundance of different metabolites at low costs that increase the chance of situation-specific effectiveness [56, 57]. Even if this approach, differing from more traditional ecological models of evolution, is being followed, this does not explain why an extremely specific, evolutionarily non-conserved, and metabolically demanding natural product such as Taxol should appear in very remote species. In any case, based on the available literature, a necessary discussion about the evolutionary-biological plausibility and the ecological classification of Taxol in fungi ultimately did not take place. It seems that for the first 20 years at least, in a frenzy of commercial exploitation, most published contributions focused on possible sources of a valuable pharmaceutical substance, but fundamental questions of biology were neglected. Sometimes even the titles of the essays seemed puffery, like: "Paving the way for a new source of this anti-cancer drug" [52]. Accordingly, the economic potential is repeatedly and ostentatiously pointed out [21, 44, 48, 49, 51, 54, 58–61].

Even more puzzling is the reputed discovery of Taxol in prokaryotes. Recently, for example, it has been claimed that bacteria synthesizing Taxol have been discovered in marine macroalgae and that the synthesis pathway has been identified [58]. Considering the effort required to prove the individual enzymatically catalyzed steps of Taxol biosynthesis, which was presumably achieved in December 2023 [34], the detection of Taxol in bacteria at least

raises questions. Another group of researchers claims to have produced the precursor of the Taxol taxadiene and taxadien-5a-ol, which is oxidized via P450 cytochrome oxidoreductases, in manipulated *Escherichia coli* with a phenomenal yield of 1 gram per liter – according to the authors' estimates, an increase in production by a factor of 15 000 [59]. The methodological approach here is not entirely transparent. This may have had commercial motives, because at the end of the paper, there is a statement that a patent had already been applied for before publication. If the results had been reproducible, one would have expected a biotechnological revolution and follow-up research focusing on how the large quantities of taxadiene could have been further processed into Taxol. However, neither happened, and, in any case, there are no publications documenting the expected academic and industrial research following the supposed discovery.

## First Doubts Arise

Perhaps there may have been doubts even then. If that was the case, they were certainly not published. At least, serious doubts about the plausibility of the fungal Taxol hypothesis arose when a research team led by Stefan Jennewein demonstrated in 2013, through genome mining, that the original fungi in question do not have the genetic make-up to produce the key enzymes of Taxol biosynthesis [60]. The article was based on the PhD thesis by Uwe Heinig. However, this fundamental caesura did not break the constant tidal wave of publications. The findings were either not noticed or ignored as healthy skepticism failed to emerge. Also, no published efforts to reproduce the original research results could be observed. It is striking that the seminal publication by Heinig, Scholz, and Jennewein was mostly – and even in broad review articles – ignored [34, 43, 44, 47, 48, 61–63], sometimes dutifully cited, but nevertheless ignored in substance [33, 44, 64]. In some cases, the article is correctly summarized in one sentence, but the negative findings have not prompted the researchers to question their own assumptions or, at least, to discuss them in more detail [8, 45, 48]. Recently, another review article was published, which outlines the individual steps of a possible biosynthesis pathway by summarizing previous findings [33] but without addressing the question of whether such a synthesis even exists in fungi.

Satisfactory answers have never been found to the obvious question of how a sterically complex product of plant secondary metabolism, in whose genesis from the terpene geranylgeranyl pyrophosphate at least 19 enzymes are probably involved, can "coincidentally" appear in extremely remote taxa from the realm of fungi. Were answers even seriously sought? The hypothesis that a horizontal gene transfer could have taken place [9, 33, 65] is extremely unlikely, especially as the enzyme-coding genes in *Taxus brevifolia* and *Taxus baccata* are not clustered [5]. There are only extremely rare cases in which plants produce microbial natural substances, like maytansinoids [66–68]. Here, however, we are talking about a transfer in the opposite direction. Even the hypothesis that the common hazel may have acquired the ability to produce Taxol from endophytic fungi [9] brings the discussion back to the initial question of whether such fungi exist at all, which is doubtful. Again, from an evolutionary point of view, the very energy-intensive synthesis of a sterically demanding natural product would be more plausible if organisms gain an advantage from it. For yews, this could be as a defense against herbivores or pests (such as parasitic fungi). But what ecological advantage could endophytic fungi derive from the complex biosynthesis of Taxol? As a highly potent cytotoxin, Taxol acts as a mitosis inhibitor on the eukaryotic cells of fungi themselves. Yews appear to store Taxol, which is also cytotoxic for them, in "hydrophobic bodies" [69, 70]. If the fungi had unknown mechanisms of detoxification [48], for example by chemically deactivating or excreting Taxol, why should they first synthesize the active substance themselves at great metabolic expense? It is possible that the endophytic fungi in the yew – depending on their own life cycle and the stage of the plant tissue surrounding them – are in a Taxol-containing environment anyway, which has not yet been clarified. In this case, however, they could also save the energy to synthesize their own anti-mitosis agent. One article investigates the extent to which a different protein sequence in the β-tubulin of endobiotic fungi could lead to a relative insensitivity to the mitosis inhibitor Taxol [62]. This may explain how fungi survive in a toxic environment of yew trees, but it would not be proof that they can produce Taxol themselves. Evolutionary-biological convergence, which has occasionally been discussed [33, 48, 65] as equivalent to the independent development of gibberellins in plants and fungi, is also highly unlikely in view of the extremely demanding and highly specific synthesis pathway. Moreover, the fungi have a selective advantage in producing gibberellins themselves, which is at least not obvious in the production of Taxol in a Taxol-containing environment. The one-sided focus on potential medical applications might have distracted the research focus from such fundamental biological questions.

## Misguided Paths and Daring Hypotheses

The gold rush has sometimes even led to some very ambitious hypotheses: for example, one research team claimed that genetically manipulated *Escherichia coli* and *Saccharomyces cerevisiae* (Saccharomycetaceae) could be brought together in a nutrient solution, each of which had imperfect synthesis pathways and could then complementarily produce an immediate precursor of Taxol [63]. A "stable co-culture" in the bioreactor was established by creating "a mutualistic relationship" or a "synthetic consortium" between the highly different species "in which a metabolic intermediate produced by *E. coli* was used and functionalized by yeast". That is more than impressive – but should this result really be taken for granted considering the questions that arise with respect to this induced "artificial symbiosis"? "Surprisingly, despite the promising initial results of their publications, no other research on the topic has been published" [9]. Really surprising? At least from an outside point of view, it seems rather unlikely that prokaryotic and eukaryotic species, each living in a completely different environment and under disparate ecological conditions, would have incomplete but coincidentally complementary synthesis pathways that would then produce a sterically complex low-molecular-weight substance together in a nutrient solution. That an organism should have developed enzymatic make-up in the course of evolution that is completely useless because it only

develops catalytic activity in a consortium with another organism with which it does not share a common habitat seems almost impossible, especially since Taxol itself has a cytotoxic effect on eukaryotic yeasts (unlike bacteria). That the P450 cytochrome oxidoreductases mentioned in the paper – out of pure coincidence – happen to complete an extremely challenging reaction chain cannot be ruled out, of course, but does not appear conclusive without further explanation. The authors of the article claim that they have transferred parts of the genetic make-up of the synthesis pathway to the two species in a modular design to optimize the oxidation of the taxadiene scaffold by *S. cerevisiae*. Nevertheless, it is assumed that the basic enzyme equipment is already present. *E. coli* was allegedly genetically engineered to produce taxadiene in excess. However, this in turn refers to an (isolated) experiment carried out five years earlier by the same team [59]. The methods of the genetic engineering remained vague, especially as the taxane synthesis pathway had not yet been elucidated with sufficient certainty at the time. Nevertheless, this work [63], whose findings appear *prima facie* implausible and – despite the huge potential benefits – have never been reproduced, was last cited in December 2023 [34].

## Shattering the Hypothesis

The detection methods available in 1993 did not yet have the precision and sensitivity of today's molecular biology and biochemistry toolbox. However, we should now know better – at the latest since a meticulous and elaborate study of a research team lead by Marc Stadler at the Helmholtz Center for Infection Research (in collaboration with experts from the Czech Academy of Sciences as part of the EU Mycobiomics project) was published in 2022 [71]. The underlying study combined methods of genome mining with morphological studies, based on genome sequence data obtained from the study of Heinig et al. [60] and type specimen that had been deposited by Strobel et al. [37] in the Farlow Herbarium at Harvard University. The study revealed that the fungus in question is – as confirmed by another source [62] – a wood-destroying basidiomycete, which makes the hypothesis of Taxol production in other fungi from the Ascomycota division appear even less plausible in terms of evolutionary biology [71]. The study concluded that contamination through the primary extraction of samples from bark or by Taxol residues in the fungi was the most likely explanation for the presumed aberrations of the Taxol hypothesis. Also, there is no shortage of refreshingly clear criticism of the quality of the numerous questionable publications of the previous decades. Unfortunately, such scientific ethos of constructive skepticism and a willingness to also publish (supposedly) negative results are far too rare – in general and very much to the detriment of science. In the few articles that have appeared since then on Taxol biosynthesis, the contribution of the Stadler team is usually overlooked [34, 62, 72] and has, at least so far, only been recognized in one publication. The article was cited in passing in a table on sequencing that had taken place, but the negative findings have not yet been recognized or discussed [33].

In fact, an unhealthy ratio between a large number of review articles and few original papers is noticeable in the breadth of publications on Taxol. Additionally, only one-off publications whose results (at least officially) have never been reproduced could be identified. Given the potential benefits of positive results, this is a conspicuous finding. Moreover, no group has succeeded in reliably detecting both the necessary DNA sequences encoding the biosynthesis enzymes and the Taxol product in fungi at the same time. The high number of publications in journals from the back ranks is striking, too. Numerous publications reveal gaps in the rationale or (perhaps also for reasons of cost) do not utilize the possibilities offered by the methods of molecular biology. Rather than focusing on scientific rigor, the main interest still seems to be directed to the potential usability and the "financial revenue".

## Scientific Negligence in Dealing with a Flood of Publications

How to explain that? We carried out a structured interview with Marc Stadler as leading mycology expert on the subject [5]. As such, he was inevitably often asked by journals to provide expert opinions in peer reviews. He reports that, as a peer review editor, some articles have crossed his desk up to five times and were repeatedly rejected by him due to serious shortcomings (namely in taxonomy and detection methods). His recommendation to resubmit the articles when an NMR spectrum for the detection of Taxol was available was never followed. Instead, texts were passed down the list, following the declining reputation and rank of the journals, and ultimately appeared in peripheral, sometimes dubious journals, regardless of their (lack of) quality. Such studies are then cited in the thicket of review articles, neither critically reviewed nor scrutinized, until they become mentally canonized. If everyone writes it, it must be true. Really? The hypothesis that, despite the large number of publications, the supposed evidence of Taxol could be nothing more than a wild pile of artefacts [65], which is not initially obvious, is actually quite plausible. After all, it is not the number of publications that should count, but the scientific quality of their findings and the robustness of their statements. A superficial evaluation of material in reviews also contributes to the effect that possible misconceptions are perpetuated. For example, the panda bear, in whose dermatitic scurf allegedly Taxol-producing fungi grow [51], becomes a "plant host" in another article [33]. Opportunities for a critical plausibility check are thus unnecessarily lost.

In the structured interview [5], Stadler explained in agreement with Heinig et al. [60] that the quantities of Taxol measured in samples that were not taken directly from yew trees (and could therefore not be contaminated with plant Taxol residues) were consistently so negligible that reliable detection would not be possible even with sensitive methods. According to Stadler, the published investigations were therefore never taken seriously by the pharmaceutical industry as promising approaches worth investing research money and time in, simply because none of the findings could be reproduced. Unfortunately, such corrections are not published by scientists from laboratories in industrial research departments. If a possible application had been discovered, this would obviously have led to an industrial implementation of the method at a larger scale and to accessory patents, which, howev-

er, never happened. One of the general shortcomings of a success-oriented publication culture is that there are few formats in which reports on failed projects or negative results can be published appropriately.

Thirty years after the supposed discovery of Taxol-producing fungi and a flood of publications, especially in the gold rush years, still no one has obtained Taxol from a fungal or bacterial culture with sufficient reliability. In the vast majority of cases of supposedly spectacular discoveries, there have also not been follow-up publications. If there was follow-up research or if there were even reproduction studies, these were at least not published. To this day, however, leading textbooks on pharmaceutical biology contain a reference to fungi that also produced Taxol [1, 7, 73, 74], albeit allegedly in insufficient yields. In this respect, the fundamental contribution from the Stadler team was also an attempt to intervene in a debate that had long since become deadlocked or even derailed, leading many scientists astray. And indeed, a lot of money and time (that could have been invested in other promising studies) has already been burnt with countless studies that may have been on an avoidable wrong track – at the latest after the seminal intervention of Heinig et al. in 2013 [60].

Immense progress in genome research with regard to the secondary metabolism of fungi [75–77] was apparently ignored, or as the Stadler team has put it: "The fact that some of these papers were published rather recently (ignoring the evidence that has accumulated on the genetics of secondary metabolite biosynthesis) causes us to question whether the reviewers and editors of the respective journals have had the necessary level of expertise to rigorously assess the submissions" [71]. This is not very flattering, but it is an apt criticism that addresses a fundamental problem of scientific communication with refreshing clarity: citations are dutifully placed, but the flood of often inadequate papers is no longer read critically and with sufficient scrutiny. More reliable evidence using NMR spectra is consistently lacking, and in one article claiming the detection of Taxol by an NMR spectrum [78], corresponding data are missing, which was rightly criticized [71]. In a recent article, an NMR spectrum is shown. However, there is no description of the method used to obtain a sample of sufficient purity [79]. The raw material must have been prepared from a sample, and the purification methods used would be crucial for the reliability of the results. It is surprising that these are not presented.

This possibly hasty approach is a general shortcoming of a scientific community driven by citation metrics [80], but it is particularly evident in the case of Taxol. Soberly viewed, despite a mountain of publications claiming otherwise, reliable evidence is currently more likely to speak against the synthesis of Taxol by fungi [81].

## Biosynthesis of Taxol Elucidated?

Nevertheless, there has been real progress in Taxol research. Previously, it was assumed that a targeted increase in yield through genetic engineering would first require the synthesis pathway of Taxol to be clarified [82]. There have been repeated attempts to elucidate this pathway [82–84], but until recently, there were still gaps in the explanation. Additionally, the bio-regulation of Taxol synthesis has proven to be at least as complex [85]. A pertinent study coordinated by the Max Planck Institute of Molecular Plant Physiology in Potsdam-Golm recently attracted attention. The interdisciplinary research team claims to have reproduced the complete synthesis pathway of Taxol in plants [34]. The individual reactions of the enzymatically catalyzed synthesis were reproduced step by step using vectors to transfer cDNA encoding enzymes from *Taxus baccata* into tobacco plants (*Nicotiana benthamiana* Domin, Solanaceae) via agroinfiltration. *N. benthamiana* has long been established as a model plant for transient protein expression by infiltration with agrobacteria. If the pathway of Taxol biosynthesis – as comprehensibly described in the thorough study – is now fully reconstructed, this will provide a basis for further research. In particular, the synthesis pathway could be made pharmaceutically applicable by means of genetic engineering methods using transgenic plants/cell cultures, a perspective also mentioned by the authors.

## Conclusion: Good Scientific Practice and the Temptations of a Gold Rush in Drug Research

We have neither the expertise nor the aim to assess the accuracy of research results and methods with regard to the question of whether there are fungi that have a biosynthetic pathway for Taxol. We are only concerned how some parts of the scientific discourse in the long Taxol story derailed. We have tried to illustrate this using the most important publications as examples. In this specific case, critical enquiries were apparently avoided for a long time, and well-founded negative findings were deliberately ignored instead of being addressed directly, straightforwardly, and constructively. Some critical observations, with regard to the specific 'grammar' of the Taxol discourse, will therefore be added. We want to combine our critical analysis with some suggestions as to how scientific integrity and standards of good scientific practice in the field of drug research can be improved.

In the case of Taxol, the mass of misleading references continued to swell from year to year. Review articles cite other review articles e.g. [8, 41, 44, 45, 52, 72], which summarize a supposed state of research in an adjusted form but ultimately only collect publications without critically questioning the sometimes incompletely substantiated or at least surprising results of the original works. Occasionally, cautious assumptions in the original contribution are cited as unequivocally positive evidence. The more citations are accumulated, the more secure and reliable a state of research appears, even though an assumption is often based on a single publication that was built on sand and never reproduced.

### Precision of citations

The primary epistemic function of the citation is to make the genealogy of an idea comprehensible and critically verifiable. Precise citation practice is therefore required. Uncertainties and open questions should be made transparent. Research methods should be carefully reviewed (and first they should be described in sufficient detail to enable research reproducibility). It is inadequate to merely reproduce supposed research results that are summarized in the abstract of an article if the article has not even been read

and the methodological train of thought has not been understood. Where only a state of research summarized elsewhere is being referenced, it should be made semantically clear that only external sources were used, and their scientific reliability was not or could not be checked. This can, of course, be legitimate, especially if evaluating a cited paper exceeds the author's own expertise. However, it should then be expressed clearly that the author does not wish to refute or confirm the referenced research results. Otherwise, there is a risk of canonizing mere assumptions or tentative interpretations into a published consensus, which is deceptive and potentially misleading.

## Interdisciplinarity

Presumably, with regard to Taxol, a too narrow and fragmented disciplinary focus has led pharmaceutical research astray. It was primarily biochemists who endeavored to isolate and detect Taxol. Biological expertise – namely from botany, mycology, evolutionary biology, and ecology – was rarely involved. Qualified control considerations of biological plausibility were made only exceptionally. In this respect, the Taxol discourse is in disarray, regardless of whether there are Taxol-producing fungi or not [5]. The purpose of a highly toxic substance produced in an energy-consuming process in a species is at least not plausible on its own, especially as, in the case of Taxol, organisms have to protect themselves against the extremely toxic effect of the spindle toxin. Thus, the "evolutionary advantage of Taxol biosynthesis in yew trees remains a mystery" [60]. It must be conceded that the ecological function of products of the secondary metabolism of plants and fungi is indeed very often unknown [86, 87]. However, the knowledge problem is probably also partly a consequence of a dysfunctional distribution of resources. Drug research, which is application-oriented and thus promises potential economic gains, can mobilize funds more easily than, for example, basic ecological research that investigates the function of a secondary metabolite, which is typically a highly specific result from a long-term evolutionary process [88, 89]. A more comprehensive perspective can help to prevent premature conclusions and provoke skeptical questions. As this case shows, even extremely specialized scientific research in the life sciences requires a healthy degree of interdisciplinarity.

## Publication of negative results

The strategies of journals to accept manuscripts for publication also require a self-critical review. With regard to Taxol, unspectacular negative results, which might not have ended the gold rush but would have slowed it down, were apparently not as attractive to journals as positive findings. While apparent successes landed in the highest ranked journals, the authors of the most important and groundbreaking contributions, which threw sand in the gears of the overambitious publication machine, had to be satisfied with specialized journals, with a visibility that is essentially limited to highly specialized professional communities. The positive and visible but, in the Taxol case, also singular exception of the high-ranking journal *Fungal Diversity* confirms the rule [60, 81]. This bias at the expense of honest skeptical research has fatal medium-term consequences for the progress of scientific knowledge. Science is reliable because it has to stand up to constant critical scrutiny, and it can potentially be falsified. Scientific knowledge acquires its epistemic rigor through the fact that it is always provisional. It is part of an evolutionary process [90]. This also includes constructive errors and their refutation. In the words of Ernst Mach, the legendary physicist and theorist of science: "The clearly recognized error as a corrective is just as conducive to knowledge as positive knowledge" [91]. High-ranking journals should honor this fact and publish seemingly unspectacular work that pours cold water on supposed successes as an equal research achievement – because those results contribute to putting research back on track.

## Avoidance of result-oriented bias

Finally, the tension between the strictly scientific, objectifying pursuit of knowledge on the one hand and, with regard to drug research, desirable medication on the other also produces an epistemic conflict of interest [92, 93] that must be addressed. The case of Taxol from fungi is an example of the dysfunctional nature of a scientific system that rewards quantity over quality and continues to pile up more and more publications (and patents) at a frenetic pace but fails to fulfil the function of science, which is to provide reliable knowledge about the world. This is the breeding ground in which bad science can thrive. If carelessness in dealing with knowledge is being normalized, an environment is created in which superficial science eventually gives birth to scientific misconduct [5]. Pharmacological and pharmaceutical research always has an inherent scientific-ethical dimension. This goes beyond the general integrity of the scientific process that must be observed in every scientific discipline. Pharmaceuticals serve to protect health and life. Pharmaceutical research is expensive, and funds are scarce. Premature assumptions that are uncritically adopted and sedimented as reliable knowledge tempt others to go astray. This costs time and a lot of money, which in the end is no longer available for other research that might have produced an effective medication or a fundamental insight. The publication of research results is therefore always accompanied by a responsibility to provide reliable findings on which other players in the research process can build. Reciprocally, special care is required when dealing with publications. Constructive skepticism and the willingness to critically question received assumptions are indispensable. Particularly where research is potentially commercially profitable, critical monitoring by the scientific community is needed to avoid one-sided distortions of perception in a pharmaceutical gold rush, which, at worst, can drift off into a hunt for a phantom.

## Contributors' Statement

Both authors (K. F. Gärditz & H. Czesnick) equally contributed to the conception and design of the work. Collection, analysis and interpretation of the data (i.e. the reviewed publications): K. F. Gärditz & H. Czesnick; drafting the manuscript: K. F. Gärditz; critical revision of the manuscript: K. F. Gärditz & H. Czesnick; drawing of the figures: K. F. Gärditz.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

[1] Teuscher E, Melzig MF, Lindequist U. Biogene Arzneimittel, 8th ed., Stuttgart, Wissenschaftliche Verlagsgesellschaft; 2020: 216–217

[2] Weaver BA. How Taxol/paclitaxel kills cancer cells. Mol Biol Cell 2014; 25: 2677–2681

[3] Yang CPH, Horwitz SB. Taxol: The first microtubule stabilizing agent. Int J Mol Sci 2017; 18: 1733

[4] Cech NB, Oberlies NH. From plant to cancer drug: Lessons learned from the discovery of Taxol. Nat Prod Rep 2023; 40: 1153–1157

[5] Gärditz KF, Czesnick H. Taxol aus Pilzen – pharmazeutische Goldmine oder wissenschaftliche Ente? Laborjournal 2023; 12–15

[6] Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. The isolation and structure of Taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. J Am Chem Soc 1971; 93: 2325–2327

[7] Sticher O, Heilmann J, Zündorf I. Pharmakognosie – Phytopharmazie. 10th ed., Stuttgart, Wissenschaftliche Verlagsgesellschaft; 2015: 958–959

[8] Sharma A, Bhatia SK, Banyal A, Chanana I, Kumar A, Chand D, Kulshrestha S, Kumar P. An overview on Taxol production technology and its applications as anticancer agent. Biotechnol Bioprocess Eng 2022; 27: 706–728

[9] Škubník J, Pavlíčková V, Ruml T, Rimpelová S. Current perspectives on taxanes: Focus on their bioactivity, delivery and combination therapy. Plants 2021; 10: 569

[10] Weaver BA. How Taxol/paclitaxel kills cancer cells. Mol Biol Cell 2014; 25: 2677–2681

[11] Barceloux DG. Medical Toxicology of Natural Substances. Hoboken (NJ), Wiley; 2008: 900

[12] Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by Taxol. Nature 1979; 277: 665–667

[13] Fuchs DA, Johnson RK. Cytologic evidence that Taxol, an antineoplastic agent from *Taxus brevifolia*, acts as a mitotic spindle poison. Cancer Treat Rep 1978; 62: 1219–1222

[14] McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, Donehower RC. Taxol: A unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med 1989; 111: 273–279

[15] Menzin AM, King SA, Aikins JK, Mikuta JJ, Rubin SC. Taxol (paclitaxel) was approved by FDA for the treatment of patients with recurrent ovarian cancer. Gynecol Oncol 1994; 54: 103

[16] Walsh V, Goodman J. Cancer chemotherapy, biodiversity, public and private property: The case of the anti-cancer drug Taxol. Soc Sci Med 1999; 49: 1215–1225

[17] Staniek A, Woerdenbag HJ, Kayser O. *Taxomyces andreanae*: A presumed paclitaxel producer demystified? Planta Medica 2009; 75: 1561–1566

[18] Martin V. Overview of paclitaxel (TAXOL). Semin Oncol Nurs 1993; 9 (Suppl 2): 2–5

[19] Aldhous P. Barking up the right tree. Nature 1991; 352: 96

[20] Much JK. Ethical issues and paclitaxel (TAXOL) administration. Semin Oncol Nurs 1993; 9 (Suppl 2): 16–20

[21] Cragg GM, Schepartz SA, Suffness M, Grever MR. The Taxol supply crisis. New NCI policies for handling the large-scale production of novel natural product anticancer and anti-HIV agents. J Nat Prod 1993; 56: 1657–1862

[22] Ketchum REB, Gibson DM. Paclitaxel production in suspension cell cultures of Taxus. Plant Cell Tissue Organ Cult 1996; 46: 9–16

[23] An Act to provide for the management of Federal lands containing the Pacific yew to ensure a sufficient supply of Taxol, a cancer-treating drug made from the Pacific yew (The Pacific Yew Act) of December 7, 1992 (16 USC §§ 4801–4804). Accessed 2024-05-02 at: https://www.congress.gov/102/statute/STATUTE-106/STATUTE-106-Pg859.pdf

[24] Wolf E, Wortman D. Pacific yew management on national forests: A biological and policy analysis. Northwest Environ J 1992; 8: 347–366

[25] Holton RA, Somoza C, Kim HB, Liang F, Riediger RJ, Boatman PD, Shindo M, Smith CC, Kim S, Nadizadeh H, Suzuki Y, Tao C, Vu P, Tang S, Zhang P, Murthi KK, Gentile LN, Liu JH. First total synthesis of Taxol: 1. functionalization of the B ring. J Am Chem Soc 1994; 116: 1597–1598

[26] Holton RA, Kim HB, Somoza C, Liang F, Riediger RJ, Boatman PD, Shindo M, Smith CC, Kim S, Nadizadeh H, Suzuki Y, Tao C, Vu P, Tang S, Zhang P, Murthi KK, Gentile LN, Liu JH. First total synthesis of Taxol: 2. completion of the C and D rings. J Am Chem Soc 1994; 116: 1599–1600

[27] Nicolaou KC, Yang Z, Liu JJ, Ueno H, Nantermet PG, Guy RK, Claiborne CF, Renaud J, Couladouros EA, Paulvannan K, Sorensen EJ. Total Synthesis of Taxol. Nature 1994; 367: 630–634

[28] Hu YJ, Gu CC, Wang XF, Min L, Li CC. Asymmetric total synthesis of Taxol. J Am Chem Soc 2021; 143: 17862–17870

[29] Walji AM, MacMillan DWC. Strategies to bypass the Taxol problem: Enantioselective cascade catalysis, a new approach for the efficient construction of molecular complexity. Synlett 2007; 1477–1489

[30] Kanda Y, Ishihara Y, Wilde NC, Baran PS. Two-phase total synthesis of Taxanes: Tactics and strategies. J Org Chem 2020; 85: 10293–10320

[31] Cordes EH. Hallelujah Moments: Tales of Drug Discovery. 2nd ed., Oxford University Press, New York; 2020: 119

[32] McChesney JD, Venkataraman SK, Henri JT. Plant natural products: Back to the future or into extinction? Phytochemistry 2007; 68: 2015–2022

[33] Subban K, Kempken F. Insights into Taxol biosynthesis by endophytic fungi. Appl Microbiol Biotechnol 2023; 107: 6151–6162

[34] Zhang Y, Wiese L, Fang H, Alseekh S, de Souza LP, Scossa F, Molloy JJ, Christmann M, Fernie AR. Synthetic biology identifies the minimal gene set required for paclitaxel biosynthesis in a plant chassis. Mol Plant 2023; 16: 1951–1961

[35] Naik S. Developments in Taxol production through endophytic fungal biotechnology: A review. Orient Pharm Exp Med 2019; 19: 1–13

[36] Stierle A, Strobel G, Stierle D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. Science 1993; 260: 214–216

[37] Strobel G, Stierle A, Stierle D, Hess WM. *Taxomyces andreanae*, a proposed new taxon for a bulbilliferous hyphomycete associated with Pacific yew (*Taxus brevifolia*). Mycotaxon 1993; 47: 71–80

[38] Stone R. Surprise! A fungus factory for Taxol? Science 1993; 260: 154–155

[39] Stierle A, Strobel G, Stierle D, Grothaus P, Bignami G. The search for a Taxol-producing microorganism among the endophytic fungi of the Pacific yew, *Taxus brevifolia*. J Nat Prod 1995; 58: 1315–1324

[40] Strobel G, Yang X, Sears J, Kramer R, Sidhu RS, Hess WM. Taxol from *Pestalotiopsis microspora*, an endophytic fungus of *Taxus wallachiana*. Microbiology 1996; 142: 435–440

[41] Zhao J, Zhou L, Wang J, Shan T, Lingyun Z, Liu X, Gao X. Endophytic Fungi for Producing Bioactive Compounds Originally from their Host Plants. In: Méndez-Vilas A (ed.). Current Research, Technology and Education Topics in Applied Microbiology and Microbial Biotechnology. Badajoz, Spain; 2010: 567–576

[42] Kumaran RS, Kim HJ, Hur BK. Taxol promising fungal endophyte, *Pestalotiopsis* species isolated from *Taxus cuspidata*. J Biosci Bioeng 2010; 110: 541–546

[43] Kumar P, Singh B, Kumar P, Singh B, Thakur V, Thakur A, Thakur N, Pandey D, Duni C. Hyper-production of Taxol from *Aspergillus fumigatus*, an endophytic fungus isolated from *Taxus* sp. of the Northern Himalayan region. Biotechnol Rep 2019; 24: e00395

[44] Li D, Fu D, Fu D, Zhang Y, Ma X, Gao L, Wang X, Zhou D, Zhao K. Isolation, purification, and identification of Taxol and related Taxanes from Taxol-producing fungus *Aspergillus niger* subsp. *taxi*. J Microbiol Biotechnol 2017; 27: 1379–1385

[45] Rai N, Kumari Keshri P, Verma A, Kamble SC, Mishra P, Barik S, Singh SK, Gautam V. Plant associated fungal endophytes as a source of natural bioactive compounds. Mycology 2021; 12: 139–159

[46] Flores-Bustamante ZR, Rivera-Ordunã FN, Martínez-Cárdenas A, Flores-Cotera LB. Microbial paclitaxel: Advances and perspectives. J Antibiot (Tokyo) 2010; 63: 460–467

[47] de Andrade HF, de Araújo ALC, da Silva MV. Screening of endophytic fungi stored in a culture collection for Taxol production. Braz J Microbiol 2018; 49 S: 59–63

[48] Kusari S, Singh S, Jayabaskaran C. Rethinking production of Taxol (paclitaxel) using endophyte biotechnology. Trends Biotechnol 2014; 32: 304–311

[49] Das A, Rahman MI, Ferdous AS, Amin A, Rahman MM, Nahar N, Uddin MA, Islam MR, Khan H. An endophytic Basidiomycete, *Grammothele lineata*, isolated from *Corchorus olitorius*, produces paclitaxel that shows cytotoxicity. PLoS One 2017; 12: e0178612

[50] Gill H, Vasundhara M. Isolation of Taxol producing endophytic fungus *Alternaria Brassicicola* from non-taxus medicinal plant *Terminalia arjuna*. World J Microbiol Biotechnol 2019; 35: 1–8

[51] Gu Y, Wang Y, Ma X, Wang C, Yue G, Zhang Y, Zhang Y, Li S, Ling S, Liu X, Wen X, Cao S, Huang X, Deng J, Zuo Z, Yu S, Shen L, Wu R. Greater Taxol yield of fungus *Pestalotiopsis hainanensis* from dermatitic scurf of the giant panda (*Ailuropoda melanoleuca*). Appl Biochem Biotechnol 2015; 175: 155–165

[52] Gallego A, Malik S, Yousefzadi M, Makhzoum A, Trémouillaux-Guiller J, Bonfill M. Taxol from *Corylus avellana*: Paving the way for a new source of this anti-cancer drug. Plant Cell Tissue Organ Cult 2017; 129: 1–16

[53] Qaderi A, Omidi A, Etminan A, Oladzad A, Ebrahimi C, Dehghani Mashkani MR, Mehrafarin A. Hazel (*Corylus avellana* L.) as a new source of Taxol and Taxanes. J Med Plants 2012; 11: 66–77

[54] Salehi M, Moieni A, Safaie N, Farhadi S. Whole fungal elicitors boost paclitaxel biosynthesis induction in *Corylus avellana* cell culture. PLoS ONE 2020; 15: e0236191

[55] Lynch M. Evolutionary Cell Biology: The Origins of Cellular Architecture. Oxford University Press, Oxford; 2024: 470–490

[56] Jones CG, Firn RD. On the evolution of plant secondary chemical diversity. Philos Trans R Soc 1991; 333: 273–280

[57] Firn RD, Jones CG. Natural products – a simple model to explain chemical diversity. Nat Prod Rep 2003; 20: 382–391

[58] Subramanian M, Marudhamuthu M. Hitherto unknown terpene synthase organization in Taxol-producing endophytic bacteria isolated from marine macroalgae. Curr Microbiol 2020; 77: 918–923

[59] Ajikumar PK, Xiao WH, Tyo KEJ, Wang Y, Simeon F, Leonard E, Mucha O, Phon TH, Pfeifer B, Stephanopoulos G. Isoprenoid pathway optimization for Taxol precursor over-production in *Escherichia coli*. Science 2010; 330: 70–74

[60] Heinig U, Scholz S, Jennewein S. Getting to the bottom of Taxol biosynthesis by fungi. Fungal Divers 2013; 60: 161–170

[61] Rai N, Keshri PK, Verma A, Kamble SC, Mishra P, Barik S, Singh SK, Gautam V. Plant associated fungal endophytes as a source of natural bioactive compounds. Mycology 2021; 12: 139–159

[62] Vélëz H, Gauchan DP, García-Gil MR. Taxol and b-tubulins from endophytic fungi isolated from the Himalayan Yew, *Taxus wallichiana* Zucc. Front Microbiol 2023; 13: 956855

[63] Zhou K, Qiao K, Edgar S, Stephanopoulos G. Distributing a metabolic pathway among a microbial consortium enhances production of natural products. Nat Biotechnol 2015; 33: 377–383

[64] Gallego-Jara J, Lozano-Terol G, Sola-Martínez RA, Cánovas-Díaz M, de Diego Puente T. A compressive review about Taxol: History and future challenges. Molecules 2020; 25: 5986

[65] McElroy C, Jennewein S. Taxol biosynthesis and production: From forests to fermenters. In: Schwab W, Lange BM, Wüst M (eds.). Biotechnology of Natural Products. Cham, Springer Nature; 2018: 145–185

[66] Yu TW, Bai L, Clade D, Hoffmann D, Toelzer S, Trinh KQ, Xu J, Moss SJ, Leistner E, Floss HG. The biosynthetic gene cluster of the maytansinoid antitumor agent ansamitocin from *Actinosynnema pretiosum*. Proc Natl Acad Sci U.S.A. 2002; 99: 7968–7973

[67] Cragga GM, Pezzuto JM. Natural products as a vital source for the discovery of cancer chemotherapeutic and chemopreventive agents. Med Princ Pract 2016; 25 (Suppl 2): 41–59

[68] Lucas DM, Still PC, Pérez LB, Grever MR, Kinghorn AD. Potential of plant-derived natural products in the treatment of leukemia and lymphoma. Curr Drug Targets 2010; 11: 812–822

[69] Solimana SSM, Greenwood JS, Bombarely A, Mueller LA, Tsao R, Mosser DD, Raizada MN. An endophyte constructs fungicide-containing extracellular barriers for its host plant. Curr Biol 2015; 25: 2570–2576

[70] Solimana SSM, Raizada MN. Sites of biosynthesis and storage of Taxol in *Taxus media* (Rehder) plants: Mechanism of accumulation. Phytochemistry 2020; 175: 112369

[71] Cheng T, Kolařík M, Quijada L, Stadler M. A re-assessment of *Taxomyces andreanae*, the alleged Taxol-producing fungus, using comparative genomics. IMA Fungus 2022; 13: 17

[72] Perez-Matas E, Hidalgo-Martinez D, Palazon J. Genetic approaches in improving biotechnological production of Taxanes: An update. Front Plant Sci 2023; 14: 1100228

[73] Wagner H, Vollmar A, Bechtold A. Pharmazeutische Biologie 2: Biogene Arzneistoffe und Grundlagen von Gentechnik und Immunologie. 7th ed. Stuttgart, Wissenschaftliche Verlagsgesellschaft; 2007: 156

[74] Dewcik PM. Medicinal Natural Products: A Biosynthetic Approach. 3rd ed. Chichester, Wiley; 2009: 227

[75] Keller NP. Fungal secondary metabolism: Regulation, function and drug discovery. Nat Rev Microbiol 2019; 17: 167–180

[76] Kuhnert E, Navarro-Muñoz JC, Becker K, Stadler M, Collemare J, Cox RJ. Secondary metabolite biosynthetic diversity in the fungal family Hypoxylaceae and *Xylaria hypoxylon*. Stud Mycol 2021; 99: 100118

[77] Cox RJ, Gulder TAM. Introduction to engineering the biosynthesis of fungal natural products. Nat Prod Rep 2023; 40: 7–8

[78] Yang Y, Zhao H, Barrero RA, Zhang B, Sun G, Wilson IW, Xie F, Walker KD, Parks JW, Bruce R, Guo G, Chen L, Zhang Y, Huang X, Tang Q, Liu H, Bellgard MI, Qiu D, Lai J, Barrero RA. Genome sequencing and analysis of the paclitaxel-producing endophytic fungus *Penicillium aurantiogriseum* NRRL 62431. BMC Genomics 2014; 15: 69

[79] Chakravarthi BVSK, Singh S, Kamalraj S, Gupta VK, Jayabaskaran C. Evaluation of spore inoculum and confrmation of pathway genetic blueprint of T13 αH and DBAT from a Taxol-producing endophytic fungus. Sci Rep 2020; 10: 21139

[80] Hirschi C. Skandalexperten – Expertenskandale. Berlin, Matthes & Seitz; 2008

[81] Niego ACT, Lambert C, Stadler M. The contribution of fungi to the global economy. Fungal Divers 2023; 121: 95–137

[82] Hezari M, Croteau R. Taxol biosynthesis: An update. Planta Med 1997; 63: 291–295

[83] Walker K, Croteau R. Taxol biosynthetic genes. Phytochemistry 2001; 58: 1–7

[84] Croteau R, Ketchum REB, Long RM, Kaspera R, Wildung MR. Taxol biosynthesis and molecular genetics. Phytochem Rev 2006; 5: 75–97

[85] Bamneshin M, Mirjalili MH, Naghavi MR, Cusido RM, Palazón K. Gene expression pattern and taxane biosynthesis in a cell suspension culture of *Taxus baccata* L. subjected to light and a phenylalanine ammonia lyase (PAL) inhibitor. J Photochem Photobiol B Biol 2022; 234: 112532

[86] Börner T. Die Toxine der Cyanobakterien. BiuZ 2001; 31: 108–115

[87] Gutzeit HO, Ludwig-Müller J. Plant natural products: Synthesis, biological functions and practical applications. Weinheim, Wiley-VCH; 2014: 81

[88] Matsuura HN, Fett-Neto AG. Plant Alkaloids: Main Features, Toxicity, and Mechanisms of Action. In: Gopalakrishnakone P (ed.). Plant Toxins. Dordrecht, Springer Nature; 2017: 243–261

[89] Langebner T. Fingerhut und Apfelbaum – zwei Pflanzen mach(t)en Karriere. Pharmakon (Eschborn, Germany) 2024; 12: 8–15

[90] Gärditz KF. The poetry of the universe, the periodic table, and the scientific progress: A review of new studies on the periodic table of the elements. Found Chem 2023; 25: 269–283

[91] Mach E. Erkenntnis und Irrtum. 3rd ed. Leipzig, Johann Ambrosius Barth; 1917: 110

[92] Kohler RE. From medical chemistry to biochemistry. Cambridge, Cambridge University Press; 1982: 284

[93] Gärditz KF. Wissenschaftsgeschichte und politisches System – Fragilität wissenschaftlicher Freiheit im Kontext. Wissenschaftsrecht 2020; 53: 59–95