Symposium contribution

Beneficial uses of plant pathogens: anticancer and drug agents derived from plant pathogens[1]

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Abstract: There are many examples, in the modern pharmacopeia, of useful medications that have been derived from plants and other living materials in the natural world. The emergence of Taxol™ (paclitaxel) as an effective treatment of ovarian and possibly other cancers has enhanced the interest of pharmacologists worldwide for the search, in the natural world, of anticancer agents and other effective remedies to combat human diseases. A promising source for known effective agents and new drugs are plant pathogens such as fungi. Recent studies have determined that a fungus (*Taxomyces andreanae* Strobel, Stierle, & Hess) isolated from the inner bark of the Pacific yew tree (*Taxus brevifolia* Nutt.) produces paclitaxel (Taxol™) and other taxanes in de novo fashion, providing an easy and possibly inexhaustible source of these important chemicals. Lichens that live on plants may also prove to contain useful chemicals, which could be exploited in modern medicine. A survey of the current literature indicates that the natural world will continue to provide such type of medications in the decades ahead, possibly from as yet unexploited sources, such as plant pathogens.

Key words: fungi, anticancer agents, Taxol™, taxanes.

Résumé : Dans la pharmacopée moderne, on trouve de nombreux exemples de médicaments utiles issus de plantes ou d'autres sources naturelles vivantes. L'apparition du Taxol[MC] (paclitaxel) en tant que traitement efficace contre le cancer des ovaires et, vraisemblablement, contre d'autres cancers a accentué l'intérêt des pharmacologues du monde entier pour la recherche, en nature, d'agents anticancéreux et autres remèdes efficaces contre les maladies chez l'humain. Les agents pathogènes des plantes tels que les champignons sont une source prometteuse d'agents efficaces connus et de nouveaux médicaments. Des études récentes ont montré qu'un champignon (*Taxomyces andreanae* Strobel, Stierle, & Hess), isolé de l'écorce intérieure de l'if de l'Ouest (*Taxus brevifolia* Nutt.), produit de novo du paclitaxel (Taxol[MC]) et d'autres taxanes, fournissant ainsi une source facilement exploitable et probablement inépuisable de ces produits chimiques importants. Les lichens qui vivent sur des plantes pourraient également contenir des produits chimiques utiles en médecine moderne. Une étude de la littérature actuelle indique que la nature continuera à fournir des médicamentsde tels types dans les décennies à venir, probablement de sources jusqu'ici inexploitées telles que les agents pathogènes des plantes.

Mots clés : champignons, agents anticancéreux, Taxol[MC], taxanes.

Introduction

It appears that science is coming full circle. Indeed, in many areas, we can look back to see the future. In this respect, pharmacology (the use of drugs to treat disease) is no exception. In the beginning, all drugs were natural, since everything we used to treat our illnesses, cure our discomforts, and protect us came from the world around us, that is from plants, herbs, and in some cases, the animal world. The first medical schools in Europe were on the main trade routes between Germany, Italy, France, and Spain and were schools of Gallenic, the precursor of pharmacy schools. The main *materia medica* taught at these schools of the 15th century (Padua, Montpellier, etc.) was the use of natural products to treat disease. This practice remained much the same for hundreds of years. Then, in this century, things began to change. Laboratory investigations led to research and the development of new drugs based on the science of pharmacology. Many important drugs were developed in the laboratory, including the antihistamines, the antianxiety and antidepressive medications, the beta-blockers, and other synthetic drugs. In fact, several Nobel prizes have been won during this century for significant drug discoveries, including synthetic drugs developed based on laboratory investigation.

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Now, we appear to be going full circle. It appears that not a week or month goes by without learning of a natural compound that has important pharmacological properties. Recent developments indicate that in the years ahead, a better understanding of the traditional use of plants may lead us back to the natural world as the main source of our medicines. Many of the antibiotics and anticancer drugs of the future will come from soils, plants, and herbs around us. One of the major sources for these medicines may be plant pathogens.

The cells of living organisms are sites of complex metabolic activities that result in the formation of a remarkable array of organic compounds, which may have inhibitory activity against microorganisms and viruses and may exhibit antitumor (cytotoxic) activity (Withering 1961). In this review, I will briefly discuss some of the important drugs, many still in use today, that come from the plant world. I will then discuss the possibility that plant pathogens become a major source of these drugs and possibly other novel chemical agents that will be isolated and studied in the years ahead.

The plant world as a source of medicine

When one looks at the modern pharmacopeia, there are many examples of drugs that were derived from plants or other componentsof the natural world. In fact, well over 40% of the drugs we currently use have their origins in the natural world. Many of these have been used for centuries and still have important uses today. In 1753, William Withering, a physician in rural England, went from town to town with his bag of medications visiting his sick patients. One day, while he was changing horses in a town, a man approached him and told him of his wife's illness. Dr. Withering went to see the woman. She had the dropsy, which we now know as congestive heart failure. Unfortunately, Dr. Withering couldn't do much about it as he was not aware of medications that could be of help at that particular time. A few weeks later, this same man approached Withering as he passed through town and told him of the amazing recovery his wife had made. Withering went to see the woman and asked what she had taken. She told him it was a "witches brew" that was prescribed for her. He asked to see the ingredients and this is where, as in all aspects of science and medicine, serendipity can play a big role. Besides being a physician, Withering was trained as a botanist. He recognized one of the 14 ingredients on the list as a plant that was very prominent in that area of England, and it turns out, in many other places in the world. This plant was foxglove (*Digitalis purpurea* L.), the source of digitalis, which we still use today, over 200 years later, for congestive heart failure. In fact, we still have not found a better drug for this use. More interesting, while we have been looking into the mode of action of this drug for many years, we are still uncertain about how it acts.

Another good example, and more recent than digitalis, is the rose periwinkle (*Catharanthus roseus* (L.) G. Don) found on the island of Madagascar in the Indian Ocean and other places around the world. About 30 years ago, this plant was found to contain chemicals with strong anticancer activity. These chemicals were then extracted and purified and the chemical composition determined. The two key drugs that were derived from this plant are vincristine and vinblastine and they are very useful in the treatment of childhood leukemia and Hodgkin's disease (Chabner et al. 1996). Even in the 20th century, when most of the medical world turned to the development of synthetic drugs, there were still some significant discoveries that came from the natural world. One of the best examples of this was the use of the bark of the willow tree (*Salix* sp.) for the relief of pain and inflammation by many first nations people and others around the world. This of course gave rise to aspirin when an enterprising German chemist synthesized this chemical for the first time in the laboratory in 1899. Since then, the little white tablets with Bayer in the sign of the cross have been amongst the top selling medications of all time. Nonsteroidal anti-inflammatory drug imitations have emerged but not replaced aspirin as a pain reliever. In fact, the use of aspirin has increased in other areas, such as anticoagulation (Insel 1996).

Fungi as a source of medicine

Equally important to drug development have been the natural chemicals found in fungi. This was made apparent by another serendipitous discovery, in 1928, by a microbiologist named Alexander Fleming, working at St. Mary's hospital in London. Fleming was in the midst of classifying a number of common bacteria when he came across probably the most significant drug discovery of all time. One of the plates on which he was growing bacteria had become contaminated with a common fungus, *Penicillium notatum* Westling. Most interestingly, on this particular plate, unlike the normal situation where the bacterial growth was distributed over the entire plate, there were no longer any bacteria present in the area where the fungus was growing. This indicated to Fleming that the fungus was producing a chemical that was destroying the bacteria. That substance was of course penicillin (Fleming 1946). The use of penicillin to combat bacterial infections took some time to come about and was due to the work of a group of investigators at Oxford University, Chain, Florey, and Abraham, who thought that this new discovery may have value as a therapeutic agent, something that Fleming did not believe was possible. Penicillin was first used in a therapeutic trial in 1941, on an Oxford policeman suffering from a serious skin infection. The drug was so precious that, after use, it was recovered from the urine, purified, and reinjected. The Oxford policeman recovered and the rest is history (Florey 1949). Many people believe that the use of penicillin reversed the war effort in favour of the allies who had the drug to treat there troops whereas the Germans did not. This led to the awarding of the Nobel prize to Fleming, Chain, and Florey for this discovery. In subsequent years, better antibiotics have been developed using the penicillin molecule and changing some of its structure to increase its stability, making it resistant to enzymatic breakdown and widening its spectrum of activity (Mandell and Petri 1996).

Through the discovery of penicillin, we had noted that fungi could be a source of chemicals for major drugs. In the years ahead, this led to another great discovery. In the 1970's, because of the well-known fact that the rainforest

and other areas of the natural world possessed some important chemicals, drug companies encouraged their scientists, when travelling to different parts of the globe, to collect samples to bring back and study for potential active ingredients. This is exactly what one of the scientists from Sandoz did when he visited Norway to give a seminar. He collected some bags of soil that contained fungal spores. The company was looking for antibacterial drugs and was in the process of looking for useful chemicals including natural chemicals. When the soil samples did not turn up anything really exciting, the bags were put on the shelf. Years later, the company decided to look for drugs that could lower the immune response to allow more successful organ transplantation and other potential uses. The bags were then taken off the shelf and one of the chemicals present was at least an order of magnitude better than any anti-immune system drug ever discovered before or since. That drug, of course, was cyclosporin, the singular reason why kidney, heart, and other transplants are so successful now compared to previously. Again, a fungus, in this case from the rainforest, had produced a very useful drug (Faulds et al. 1993).

New drug discoveries in the plant world

From what we have seen in the past few years, there is every reason to believe that the key drugs in the years ahead will also come from the natural world. If the past few years are any indication, we are in for some more exciting discoveries. One of the recent discoveries, the taxanes paclitaxel (Taxol™) and docetaxel (Taxotere™), are the most promising new chemotherapeutic agents developed for cancer treatment in the past decade. These chemicals are found in high concentrations in the bark and other parts of the Pacific yew tree (*Taxus brevifolia* Nutt.). Taxol™ has already shown very effective against ovarian and breast cancer and recent clinical trials have shown that paclitaxel and docetaxel may also be useful agents in the treatment of non-small-cell lung cancer, head and neck cancer, and other types of cancers (Suffness 1995). The problem is that the amount of the taxanes needed for each cancer treatment may require kilograms of bark tissue. Therefore, other ways to exploit the value of this chemical have to be found. The structure of Taxol™ is very complex and, for a long time, this impeded the chemical synthesis, an alternative to using the natural source. It has recently been accomplished (Stierle et al. 1995). Yet, it is very time-consuming and difficult, requiring 23 steps, and thus is not practical, at present, as an alternative to the natural source.

Another method being investigated to increase the amount of Taxol™ available is plant cell culture. The potential of this method is significant, particularly in combination with likely future developments in the biosynthesis and cloning of genes from the biosynthetic pathway. This technique may work, but is complicated by the complexity of the chemical to be produced. A semisynthetic process with a precursor from the leaves of the English yew (*Taxus baccata* L.) is currently in use but the search continues for sources that will provide this chemical at large concentrations, which will be required in the years ahead (Suffness 1995).

Plant pathogens as a source of drugs

There are a number of fungi, which are plant pathogens, that may become a rich source of drugs in the future. A major contributor may be fungi that invade the bark of the Pacific yew tree. It has recently been discovered that not only is paclitaxel found in the bark but that a fungus, *Taxomyces andreanae* Strobel, Stierle, & Hess, isolated from the inner bark of the Pacific yew tree appears to produce paclitaxel and other taxanes in de novo fashion when grown in semisynthetic liquid media. The harvesting of this fungus could yield an important source of Taxol™ and possibly other anticancer agents. This is especially significant as it appears that the fungus would be an easier source of Taxol™ than harvesting of the bark and possibly less time-consuming and costly than either chemical synthesis or genetic engineering. In the years ahead, this microbial source could provide an inexhaustible supply of Taxol™ and novel taxanes (Stierle et al. 1995) for the treatment of cancer.

It has also been discovered that *Aspergillus fumigatus* Fres. and *Rhizomucor pusillus* (Lindt) M.A.A. Schipper, two of the most common thermophilic fungi found in hazelnut (*Corylus avellana* L.) and walnut (*Juglans regia* L.) seeds, may be a good source of chemicals that could be exploited as drugs, such as zearalenone (Abdel-Hafez and Saber 1993). *Penicillium* mold has been found to be present on oranges and possibly other fruits and could be exploited as a source of penicillin and other chemicals. In addition, fungi such as *Claviceps purpurea* (Fr.:Fr.) Tul. are one of the oldest known producers of mycotoxins with central nervous system activity, including ergotamine and lysergic acid derivatives (Gröger 1972).

Lichens that live on plants may also prove to contain important chemicals, which could be used in modern medicine. Lichens are symbiotic organisms consisting of fungi and algae, which produce a large number of acidic organic products in significant quantities. Numerous compounds isolated in the last few years from lichens have proven to be effective antimicrobial agents belonging to several distinct chemical classes, including polysaccharides (mainly glucans) having host-mediated antitumor action, lactone derivatives with antibacterial activities, and orcinol and β-orcinol depsides and depsidones representing the class with most numerous lichen antibiotics. Usnic acid, the most widely distributed and best known lichen antibiotic, has been used in several countries as a topical antibiotic for human skin diseases (Bérdy et al. 1982).

What are the kinds of drugs we are looking for, that the natural world, and possibly plant pathogens, may yield? New, better, and more effective drugs are mostly needed against bacterial and viral infections as well as anticancer agents. The anticancer drugs we have at present possess numerous side effects and are not effective against many forms of cancer. There are a few antiviral drugs available thathave proven to be valuable in the treatment of human disease, but there are many viruses that we still cannot combat effectively with drugs, including the common cold viruses and more serious infections such as AIDS. In the areas of antibiotics, arguably, there has not been a significant new class of effective agents produced in over 20 years.

Conclusion

Pharmacology has greatly benefited from uncovering and utilizing the chemicals of the natural world. From the early days and into the present, this source of new drugs has played a significant role. In the years ahead, plant pathogens may provide a useful source for many known effective pharmacological agents as well as a source of novel chemicals that will enhance our ability to treat bacterial and viral infections as well as cancer.

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