A review of several anticancer chemicals derived from natural medicinal plant

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Abstract:

Humans have used natural plants and plant-derived medicines to cure various diseases for thousands of years. Of all the diseases that humans are facing, cancer is one of the most destructive ones. Scientists have studied anticancer chemicals from natural plants for decades, and some chemicals show significant effects against cancer and are applied widely in clinical use. Vinca alkaloids are a type of chemical derived from Catharanthus roseus. Members of the vinca alkaloids have been used in many chemotherapy regimens. Taxol is one of the most famous plant-derived medicines against cancer. Scientists have focused more than twenty years on improving its synthesis route. Solanine comes from plants in the genus Solanum. This kind of plant is used in TCM for cancer treatment. Apart from these land plants, marine plants and marine photosynthetic algae are also sources of antitumor agents. Carrageenan and Fucoidan are two examples of antitumor-active compounds derived from seagrass. They have both cytotoxicity and adjuvant ability. In the future, there will be more research on the improvement of the synthetic route of existing herbal compounds, the discovery of new herbal compounds, and the better utilization and combination of herbal compounds, and finally lead to better application of natural plant medicine against cancer.

Keywords: cancer, natural medicinal plant, vinca alkaloids, taxol, marine algae.

1. Introduction

Natural herbal medicine has always been an important part of human history. As ancient as the Mesopotamian civilization, more than 4000 years ago, there were documents using the oils of Cedrus species and other plants, which are still used in modern medicine.[1][2] Around 1500 BC, the Ancient Egyptian word “Ebers Papyrus” documented many remedies. Many of these remedies include plants as part of the drug and treatment.[3] One of the most significant systems of plant medicine is the Traditional Chinese Medicine (TCM). The vast majority of the medicines in TCM are parts of plants, though some medicines are from animals and fungi. Many important books from hundreds to a thousand years ago have directed diagnoses and treatments in ancient China. They still play a critical role in the medical field in modern China. Currently, many people are focusing on developing plant-derived medicines that could treat one of the most destructive diseases for humans: cancer.

Cancer begins with a tumor. There are two important processes involved in the development of tumors in cancer. Angiogenesis is the process of tumor cells excreting certain chemicals called tumor angiogenic factors (TAFs), and these factors trigger the endothelial cells of neighboring blood vessels to grow and divide until new blood vessels form that connect the original blood vessels to the tumor.[4] The new blood channel could provide the tumor with nutrients. Metastasis is the process of the tumor to proliferate and invade other places of the body, forming a malignant tumor. Malignant tumors can cause many devastating effects on the body, and these diseases can be called a joint name: cancer.

In 2020, it was estimated by GLOBOCAN that there were about 19.3 million new cancer cases worldwide. Traditional methods to treat cancer include chemotherapy and radiotherapy. They could destroy tumors effectively, but they also have huge side effects. Patients usually suffer from nausea, frequent emesis, and loss of appetite. These side effects are grueling, and they could be long-lasting. Furthermore, recent clinical researchers have noticed that some traditional medicines used for chemotherapy are less effective because of the development of drug resistance.[5] For these reasons, there is an urgent request of the modern medical field to develop new drugs, along with new methods of treatment, to reduce the pain of patients and deal with drug resistance.[6]

It is not a new idea to utilize plants to treat cancer. Native Americans and Asians have used the natural plants in the genus Podophyllum to treat skin cancer.[7] From the genus Podophyllum, scientists have extracted etoposide and teniposide, two chemicals used to deal with cancer.

Along with etoposide and teniposide, many other chemicals derived from natural plants are also in clinical use or are researched for future application. These chemicals are mostly secondary metabolites of plants.

These secondary metabolites are produced for plants as their reaction toward different environmental stress and have functions including self-defense against predators. This makes many secondary metabolites have the property of cytotoxicity, which may also target certain tumor cells. Thus, secondary metabolites serve as the main objectives in discovering herbal medicine against cancer.

This essay will briefly introduce some of the most important history, mechanisms, applications, and futures of herbal compounds. This essay will also focus on chemicals derived from marine plants. Marine algae will also be included in this essay, though usually they are not included in Plantae. Then, the author will give an outlook on the probable future development of natural plant medicine.

2. Important herbal chemicals

2.1. Vinca alkaloids

2.1.1 Description

Vinca alkaloids, including vinblastine, vincristine, vindesine, and vinflunine, are derived from precursors extracted from Catharanthus roseus.[8] However, acquiring these chemicals naturally was inefficient and had a low production rate.[9] Research has been made to seek improvements in the production of vinca alkaloids and various methods have been used. Sidkey's research showed that it is possible to increase the production of secondary metabolites of Catharanthus roseus by increasing the growth factor and thus increasing the yield of needed vinca alkaloids.[10] New methods of vinblastine production are also studied, including using microorganisms as the instrument of production.[11]

Vinblastine and vincristine, along with other vinca alkaloids, are some of the earliest and most commonly used naturally derived chemicals against tumors. They are effective agents in chemotherapy against lymphomas and are employed in hematological cancers.[12][13] They also worked with other chemicals and formed many widely applied chemotherapy regimens to treat Hodgkin lymphoma.[14][15] The survival rate of Hodgkin lymphoma has increased significantly in the past few decades, thanks to the chemotherapy regimens, which almost all include vinca alkaloids. Among them, one classic and widely used combination is ABVD, which includes adriamycin, bleomycin, vinblastine, and dacarbazine.[16][17] Other regimens for Hodgkin lymphoma and non-Hodgkin lymphoma include MOPP (the first successful regimen for Hodgkin lymphoma), BEACOPP, CHOP, and Stanford V.[18][19][20][21] Vinca alkaloid, vinblastine, or vincristine (oncovin) appear in these regimens.

2.1.2 Function

Vinblastine is one of the anticancer drugs that targets microtubules.[22] Microtubules are a kind of cytoskeleton that plays a critical role in the mitosis of cells. During the mitotic phase of the cell, spindle fibers, composed of microtubules, are responsible for the separation of chromosomes. Without microtubules, mitosis would be halted, and the cell could not divide, which will trigger the process of apoptosis. Because the unlimited dividing of abnormal cells causes the tumor, preventing these cells from further mitosis is one of the most obvious and effective ways to stop the tumor from progressing. As a result, much research about chemotherapy drugs has been focused on chemicals that could change the activity of microtubules.

According to Panda et al., 0.1 to 0.4 microM vinblastine could cause the more active side to be stable and the more stable side to be depolymerized.[23] As a result, with effects on both sides, the microtubules of the targeted cell will behave abnormally and cause the cell to be arrested in the mitotic phase. It is also worth noting that at lower concentrations of vinblastine, the spindle fibers are not depolymerized but changed into abnormal forms. According to research by Jordan et al., the abnormality of spindle fibers could be divided into four levels, from looking like normal spindle fibers to literally no microtubules but only tubulins, the building block of microtubules. From 0.2 nM to 6 nM of vinblastine, the proportion of cells with higher damaged microtubules increases.[24] In low concentrations like 0.4 nM, most spindle fibers are normal or almost normal. This finding might be useful in the clinical application of vinblastine, as patients who receive this drug may face side effects that might be severe to some people.[25] When using it clinically, it is worth considering that to certain people, the dose might need to be decreased compared to normal use for their safety. With the research of Jordan et al. and other related researchers, it might be easier for physicians to decide the amount of drug to be used for each patient, which could both reach satisfying results against tumor cells and also be conservative enough that the dosage won't harm the patient severely, considering that it is inevitable to have a certain amount of side effects.

2.2 Taxol

2.2.1 Description

A more common and widely used plant-derived chemical is paclitaxel or taxol. Paclitaxel is extracted from the bark of the tree Taxus brevifolia, whose genus, Taxus, gave the chemical its name.[26] Though first discovered in the 1960s, taxol was not widely tested experimentally and

clinically because of its low extraction rate: 50-150 mg/kg from natural sources.[27][28] Almost twenty years later, GuBritte-Voegelein et al. discovered certain chemicals, like 10-deacetylbaccatin III and baccatin III, that could be easily acquired from some natural plants, and those substances could serve as precursors for the production of taxol. The discovery allowed a relatively mass production of taxol and significantly increased its availability for experimental and clinical application. Since its first clinical discovery of its activity against ovarian cancer, paclitaxel has played critical roles in the treatment of various cancers, including breast cancers, small-cell and non-small-cell lung cancers, and colorectal cancers.[29]

The search for improving the route of synthesizing taxol never stops. In 1994, Holton's group finished the first total synthesis of taxol.[30] Almost simultaneously, Nicolaou's group also finished the total synthesis of taxol.[31] From then on, more research was conducted, and new processes were being found. Recent innovations in total synthesis include the two-phase synthesis by Baran's team in 2020 and the asymmetric total synthesis by Chuang-Chuang Li.[32][33] Many efforts have been put into studying the production of paclitaxel, and more research is still being conducted. It is foreseeable that after the endeavor of countless research studies in the past, now and in the future, paclitaxel will have easier and cheaper ways of production, be able to be applied more extensively in clinical use, and contribute more to the fight against cancer.

2.2.2 Mechanism

The mechanism of taxol against tumors is quite special. As a chemical that targets microtubules, taxol, unlike vinblastine and colchicine, significantly promotes the buildup of microtubules from tubulin.[34] As a result, the previously normal concentration balance between microtubule and tubulin is destroyed. Thus, the cell division cycle is blocked, and programmed cell death, or apoptosis, is triggered.[35] Recent research has also noticed that paclitaxel causes mitotic arrest and induces the hyperphosphorylation of Bcl-2, a protein that controls apoptosis. [36] This might also contribute to the final apoptosis that taxol induces.

2.3 solanine

Solanine is a kind of natural steroid alkaloid that was first extracted from Solanum nigrum Linn. Then, it was extracted from Solanum tuberosum Linn, or cultivated potato.[37] It also appears on immature Solanum melongena L. and Solanum lycopersicum L. α-solanine is a kind of steroidal glycoalkaloid, which is the product of the secondary metabolism of plants and serves as a defensive chemical of the plant against attacks from insects and pathogens.[38] As a result, many glycoalkaloids(GAs) has toxicity that has caused severe effects on human. However, the toxicity of α-solanine itself is not as severe as other GAs like chaconine. [39] Normally, eating potatoes won't make people get poisoned, as α-solanine concentration is low in mature potatoes. Immature potatoes, however, have significantly more α-solanine than mature ones, so eating immature potatoes could be risky. Besides its toxicity, another property makes α-solanine being focused on by countless researchers: its bioactivity against tumors. In Traditional Chinese Medicine (TCM), Solanum nigrum Linn, as well as other natural plants, has been used to treat tumors. This method is named Gubenyiliu II (GYII) and is an effective method often used together with chemotherapy. Clinical practices have shown that GYII could make chemotherapy less destructive to patients.[40] GYII also shows inhibiting in the proliferation of various cancers, including breast cancer, laryngeal cancer, and pancreatic cancer.[41][42][43] Recent studies have focused on the extractive from traditional plant medicines. A study conducted by Li et al. focused on a combined drug of Astragaloside IV, α-solanine, neferine, and 2,3,5,6-tetramethylpyrazine, which they named SANT. All these four chemicals are derived from herbal medicines used in the GYII method. Their research showed that SANT shows obvious inhibition of Heparanase (HPSE), an enzyme that plays a critical role in the angiogenesis and metastasis of tumors. [44] Angiogenesis and metastasis are two crucial parts for a newly born tumor to grow into the aggressive version that could be fatal to a human, so blocking or retarding these two processes would slow down the progression of the tumor and the deterioration of cancer development. SANT inhibits the enzyme that promotes tumor angiogenesis and metastasis; thus, it has the potential to serve as a very effective drug against cancer. It is worth noting, though, that there isn't much research about SANT, and we lack enough studies about how to apply SANT safely, so there might be some more efforts and studies that could contribute to making this promising method into clinical use.

2.4 Chemicals from natural marine plants

This essay has introduced some typical natural chemicals gained from land plants. Apart from them, aquatic plants are also worth noting. Though many aquatic biomes high in biodiversity are freshwater, like marshes and swamps, saltwater, especially marine ones, should also not be neglected. Though most of the marine plants are only limited to the upper part of the ocean, subject to the insufficiency of sunlight in the deep sea, the

ocean occupies more than two-thirds of the world's surface. Marine biomes, such as coral reefs, and other diverse coastal saltwater biomes, like salt marshes and mangrove forests, are also abundant in genetic and species diversity. Although only about 0.085% of total identified angiosperms live in marine environments, and there is only one group of submerged marine angiosperm, which is the seagrasses, there have been various studies that showed the application and potential to extract drugs that could treat various diseases from these marine angiosperms.[45][46] There are also no bryophytes and little other vascular plant.

Despite the absence of higher plants, the ocean contains numerous prophlorophytes and algae. These plants are relatively primitive (can't even strictly be called "plants" because they are not in Plantae) compared to vascular plants, but their potential in cancer treatment is no less than other plants. Though the research of clinical and pharmaceutical applications is not as abundant as those of terrestrial vascular plants, and most medicines derived from oceanic plants are in the preclinical and early clinical development stage, marine natural products have shown significant activities. They cast a promising future of application in various medical fields, including in the treatment of cancer.[47][48]

2.4.1Carrageenan and fucoidan

The ocean is abundant in algae, especially red and brown algae. About 98 percent of the red algae on Earth are oceanic, and about 99 percent of all brown algae live in the ocean. From these photosynthetic algae, people extracted many bioactive chemicals. Among them are carrageenan, derived from red algae, and fucoidan, from brown algae.

Carrageenans are a polysaccharide in many kinds of red algae, including Eucheuma, *Kappaphycus*, and Chondrus genera species.[49][50][51] It was first discovered in Irish moss, Chondrus crispus, and many other species.[52] Some species are then artificially cultured to supply for the carrageenan industry. Carrageenans are extracted from these red algae's cell walls, and most carrageenans are rich in sulfate, except beta-carrageenan.[53] Carrageenan is a multifunctional agent in the medical field and thus is applied widely. It could serve as an antioxidant, anticoagulant, anti-viral agent, anticancer agent, etc. Its medical properties are also applied commercially. For example, research about using its inhibitory ability against human papillomavirus in producing carrageenan-derived sexual lubricants and infant feeding formulas.[54]

Among these properties, one noteworthy ability of carrageenan is its efficacy against cancer. Besides medical use, red seaweeds are viewed to enhance human resistance to tumor progression as a kind of food, which might be because of their antioxidant activity.[55] For carrageenan, its antitumor property could function in two ways. The first way is that carrageenan could enhance the immune response against tumors or immunomodulation. In an in vivo experiment, the injection of λ-carrageenan into mice tumor cells inhibits melanoma B16-F10 and mammary cancer T1 tumor growth by inducing the activation of M1 macrophages, dendritic cells, and cytotoxic and helper T cells. [56] This experiment also showed that λ-carrageenan could also act as an adjuvant for OVA-based vaccine, which means that λ-carrageenan could also play a helping role in immunotherapy of cancer. This method of inducing the patient's immune response against cancer is one of the hot topics of cancer treatment research. Though it might not be effective enough to eliminate the tumor alone, combining it with other therapeutic methods could make it more effective and beneficial to the patients.[57] This combining concept is especially important in developing carrageenan-based drugs because it has another function. Carrageenan also has cytotoxicity, meaning it could be used directly in chemotherapy. According to research, a nanocomposite made of ι-carrageenan-γ-maghemite could arrest cancer cells in the G2/M phase and induce apoptosis.[58] Another research found out that κ-selenocarrageenan, a molecule that has selenium acid groups partially replacing the sulfate acidic groups of κ-carrageenan replaced by selenium acid groups, could arrest human hepatoma cells on the S phase and then trigger apoptosis.[59][60] Its cytotoxicity is highly specialized, meaning it will only affect the cell cycle of cancer cells.[61] It is worth noting that carrageenan is not completely harmless. According to in vivo experiments, orally administrated carrageenan could cause colitis in animals.[62] As a result, there might be more clinical research to determine the side effects of carrageenan as an antitumor agent on humans, and the practical use of carrageenan should consider its side effects.

Fucoidan, or fucan or sulfated fucan, is mainly composed of L-fucose, and it is derived from the cell wall of many kinds of brown algae, though it is also present in marine invertebrates. [63] Fucoidan also has many medical functions, like antithrombotic, anti-viral, and anti-inflammation.[64]

The functions of fucoidan against tumor cells are somewhat similar to the functions of carrageenan. Fucoidan could both directly trigger the apoptosis of tumor cells and act as an adjuvant for cancer therapy.[65] Researches showed that fucoidan could induce HCT116 human colon cancer cells to be arrested at G1 phase, and then cause apoptosis.[66] More interestingly, this experiment showed that this cell arrest is independent

of the p53 tumor suppressor, which means that fucoidan might be a solution to tumor cells that could not be treated by targeting p53. Other research also showed that the cytotoxicity of fucoidan is specific and could even protect normal cells from apoptosis.[67] Fucoidan also takes part in immunomodulation by increasing the activity of macrophages.[68] As macrophages are activated, they could trigger NK-cell-mediated apoptosis targeting tumor cells.[69]

3. Outlook

Though there are factors that have restricted the development and application of natural plant medicine, the future is still bright and promising. Many researchers have focused on improving the route of synthesis of different kinds of chemicals that have been put into use, especially biosynthesis, an efficient and environmentally friendly method. These two characteristics, especially the method's impact on the environment, should be the most prioritized consideration, as sustainable development is the topic of the recent world.

Another important field that many researchers have been dedicated to is finding new chemicals and new applications of known chemicals. Many currently used substances are derivatives of chemicals that have been discovered before. As a result, it is suggested that in the future, more research on finding other analogs of the substances that people now discover could be a hopeful way of finding some new effective derivatives. Some of them might be easier to acquire while having similar pharmacological activities. In contrast, others are the relatives more efficient against the same target or have fewer side effects.

In finding new herbal chemicals, the aquatic ecosystems should never be neglected. Because of the difference between aquatic and terrestrial biomes, the ocean has an even larger potential for drug discovery than land. In the ocean, the environmental conditions are different, which causes different environmental stressors to the oceanic plants, such as high salinity, ocean currents, and insufficiency of nutrients.[70] The biotic stresses, such as predation and competition, are also very different from those on land. This could be critical to discovering novel medicines because facing different stresses means that the plants will likely have different functional secondary metabolites, which are new possibilities for drug discovery. Not to mention the difference between the plant types in the ocean and that on land.

To ensure that there are still exploitable plant resources for medicine, though, the protection of the environment should also be implemented as completely as possible. The destruction of many ecosystems will cause the loss of various habitats, which will further cause many plant species to die out. With fewer species existing, fewer potential drugs could be discovered. The ocean, for example, only has 2.9% of its area highly protected, and wetlands, which are some of the most biologically diversified ecosystems, are facing rapid decline in the area.[71][72] Not to mention the high deforestation rate. Although many developed countries have established relatively thorough legislation for protecting the environment, and many projects have shown significant preserving outcomes for fragile habitats and endangered species, a more important aspect of preservation, especially from the aspect of drug discovery, is the protection of the environment in less developed and remote regions. This is because many plant species in these areas have not been examined for their secondary metabolites for bioactivity, and many of them are not even identified. Many plant species in these areas have become extinct before people recognize and examine them. Some of these plants probably include chemicals that have bioactivity against tumor cells. To avoid such tragedies in the medical field in the future, the protection of the environment in all places around the world should be implemented as soon as possible.

Besides discovering new ones, applying the current ones in advanced methods is also one of the researchers' focuses. Some chemicals could be used together to better deal with cancer. Different medicines have different effects on the tumor. Combining these chemicals could make the treatment more effective, as the combined drug attacks the tumor in various ways. Some drugs, however, might interfere with each other, reducing the result of treatment and might even be hazardous to the patients. As a result, research needed to be conducted to ensure the combinations were effective and safe.

It is also worth noting that learning from our ancestors might surprise us in finding new drugs -utilizing and improving the traditional medicine system. GY II is a great example of using TCM in the modern medical field, and Asians and Americans have long been using plants to treat cancer. Their methods are theories that might not be verified scientifically but have been proven effective by countless lives, generation by generation. As a result, we could use our ancestors' gathered wisdom and improve them using modern science. When developing these medicines and all kinds of medicine, it is also important to have enough research and experiments to ensure that they show enough activity and, more crucially, show acceptable side effects.

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