

Application of Paclitaxel in Ovarian Cancer and Effect of Different Administration Methods

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Abstract. Paclitaxel, which acts on the spindle apparatus to kill cancer cells, as a classic drug for cancer treatment, has attracted people's attention in the application prospect of ovarian cancer. In the aspect of synthesis, currently, paclitaxel is obtained by natural synthesis and artificial synthesis. The yield of natural synthesis is not good. Artificial synthesis has a high conversion rate, but it still needs to reduce the synthesis steps and increase the yield. In terms of drug intake, the side effects of injection can be reduced by oral administration instead of prolonged injection time. As for the side effects of the drug itself, although there are still many side effects caused by the use of taxol to treat ovarian cancer, the effect can be improved by combining it with natural drugs. From the synthesis, medication methods and clinical problems of paclitaxel, the current prospects and problems in the application of paclitaxel were analyzed comprehensively, and the conclusion was drawn that paclitaxel is a drug worth using and expected to be improved at the present stage.

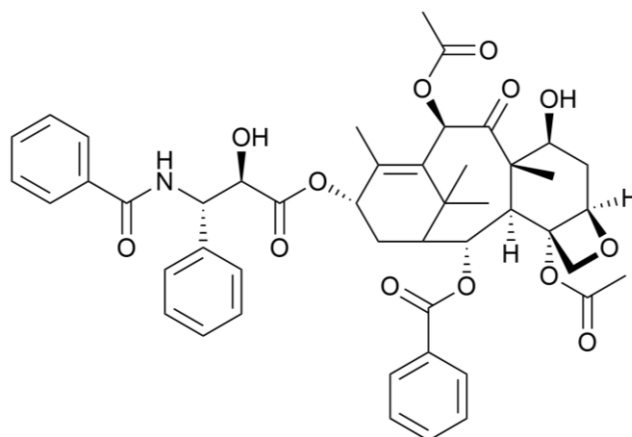
Keywords: Paclitaxel, Ovarian Cancer, Nanocarrier, Oral Preparation, Clinical.

1. Introduction

Under the current medical and medicine standard, cancer is still one of the diseases that humans are eager to conquer at present. In the United States, 5,670,535 patients with malignant cancers died from 2005 to 2014, according to a study in the paper [1]. Ovarian cancer (OvCa) is one of the leading causes of cancer death in women in developed countries, which is a malignant tumor that is difficult to detect in early stage, difficult to diagnose in late stage, and has high morbidity and mortality in women. Quality treatment for OvCa includes tumor debulking surgery and intravenous platinum-based therapy. Many patients can achieve remission after treatment, but the possibility of relapse is always high because of drug resistance. Until now, paclitaxel has been developed in multiple formulations. However, to be widely used as a drug, paclitaxel requires many aspects, such as cost-effective synthesis, excellent clinical performance, few adverse reactions and so on. This essay will combine the current synthesis method of paclitaxel, clinical effect, current application, and adverse reactions to provide a reference for the future exploration of paclitaxel in the treatment of ovarian cancer, so that it has a more scientific, flexible and broader prospect.

2. Structure of Paclitaxel

Paclitaxel is usually a white crystal powder under constant temperature, which empirical formula is $C_{47}H_{51}NO_{14}$. The structure of paclitaxel is shown in the Figure 1. The density of paclitaxel is $1.4 \pm 0.1 \text{ g/cm}^3$ and its molecular weight is 853.906 g/mol. The boiling point and freezing point are $957.1 \pm 65.0^\circ\text{C}$ and 213°C under a standard atmosphere. Paclitaxel is generally insoluble in water ($<0.1 \text{ g/L}$), but it can be dissolved in DMSO (dimethyl sulfoxide) ($\geq 31 \text{ g/L}$). When paclitaxel is untreated, it is highly toxic to the skin, respiratory tract, eyes and germ cells. It can irritate these relevant organs and can be fatal in severe cases.



(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester

Figure 1. The structure of paclitaxel

3. Mechanism of Paclitaxel

Paclitaxel can function in the process of cell division of spindle microtubule protein, divided into α -tubulin and β -tubulin. It can be combined into specific areas of the microtubule protein in the cancer cells which have the effect of preventing the depolymerization and cells will accumulate a lot of tubulins. The result of that is the cancer cells within the tubulin synthesis spindle microtubules cannot quickly in the process of cell division and the cell division stays in G2 and M phases of the whole cell cycle forever, which leads to the failure of replication and division of cancer cells. Finally, paclitaxel leads to the apoptosis of cancer cells, thus plays the role of killing cancer cells.

4. Preparation

At present, the synthesis of paclitaxel is mainly divided into natural extraction and artificial synthesis.

4.1. Natural extraction

There are two natural extraction methods which are plant extraction and bacterial culture method.

4.1.1. Plant extraction

Paclitaxel can be extracted from the bark of a slow-growing taxus in the western part of the Atlantic in modest quantities, reaching only 0.01% of the dry weight of the bark [2].

4.1.2. Bacterial culture method

Now, a fungal endophyte (*Taxomyces Andreanae*) that lives in pacific yew's phloem has been found to produce paclitaxel and related compounds [3]. There are two kinds of ways. One is in a semi-synthetic liquid medium to grow and produce paclitaxel [3], which can be induced by the addition of methyl jasmonate to *Taxomyces Andreanae* to synthesize paclitaxel [4]. Another way is semicontinuous perfusion nodule culture. However, at present, the yield of these methods is still not very ideal [5, 6].

4.2. Artificial total synthesis

Nowadays, there are several ways in chronological order to synthesize paclitaxel, including: Nicolaou synthesis (1993), Holton synthesis (1994), Danishefsky synthesis (1996), Wender synthesis (1997), Mukaiyama synthesis (1998), Kuwajima synthesis (2000), Takahashi synthesis (2006), Sato-Chida synthesis (2015), and Nakada synthesis (2015) [7]. The above methods of synthesis were

usually through continuous improvement and optimization of the previous method of synthesis to achieve better results and higher efficiency. In the synthesis of paclitaxel, there are many problems to be solved, among which how to synthesize eight-membered carbocyclic ring is one of the most important problems. In Nakada Synthesis, this problem is effectively improved by a catalytic method called Pd-catalyzed methyl ketone intramolecular alkenylation, by which the cyclization yield can be increased to 97 percent [8]. The reaction process is shown in the Figure 2. At present, the existing synthetic methods have a comprehensive process and acceptable yield, but still need to simplify the synthesis steps and increase the yield.

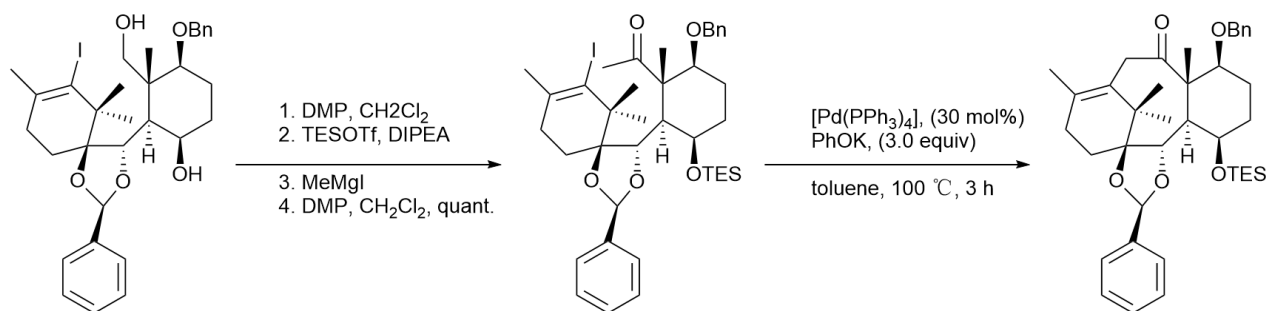


Figure 2. The reaction process of cyclization

5. Injectable paclitaxel delivery system

5.1. Paclitaxel injection

As a routine treatment of ovarian cancer with agent, the PTX injection is commonly used in a line of advanced ovarian cancer and subsequent treatment. PTX solubility in water is poor, the general will join cremophor EL and ethanol injection to increase the solubility of PTX, but cremophor EL will cause an allergic reaction, toxic reaction and vasodilatation and other serious adverse reactions [9].

5.2. Docetaxel injection (DTX)

DTX is a semi-synthetic paclitaxel drugs, compared with PTX, its water solubility is larger, lower toxicity, has good bioavailability, studies confirm the antineoplastic activity of DTX stronger than PTX, and PTX no cross resistance. Dosage forms are listed for the treatment of ovarian cancer only for injection, but in recent years on the solubility of DTX, toxicity, targeting and stability properties, preparation of related research including Emulsion, liposomes and nanoparticles and micelle.

5.3. Paclitaxel liposome injection

PTX was wrapped in a class of lipid bilayer liposome particles, a kind of cell structure, significantly improve the solubility in water, can effectively reduce drug treatment dose and reduce drug toxicity, improve patients' tolerance [10]. Clinical first-line chemotherapy for ovarian cancer and metastatic ovarian carcinoma after treatment. If the PTX and P-gp inhibitor coating to the combination of transferrin in liposomes, targeted in ovarian cancer cells of high load, high efficiency cell toxicity and drug resistance reversal aspects show better response [11].

5.4. Albumin-bound paclitaxel injection (new paclitaxel nanoparticle)

Albumin-bound paclitaxel is a novel dosage form of paclitaxel, which combines endogenous human blood albumin with paclitaxel in a non-covalent form. The prepared nanoparticles completely overcome the disadvantage of paclitaxel insoluble in water, and do not need cremophor EL or Tween-80 as co-solvent. As albumin is an endogenous natural product, it has the advantages of safety, non-toxicity, no immunogenicity, biodegradation and good biocompatibility [9].

6. Non-injectable paclitaxel delivery system

Traditional paclitaxel injections require the addition of surfactants to increase their solubility, which is associated with many serious adverse reactions. In recent years, albumin-bound paclitaxel injection as a new generation PTX delivery way was gradually promoted and used in ovarian cancer treatment and got good treatment effect. However, long intravenous infusion leads to poor patient compliance and high price, which is not the best choice for treatment [10]. Present, PTX drug delivery dosage form is not only confined to the injection dosage forms, there are more than injection way, such as oral and vaginal drug delivery, etc., using the advantage of these different ways of drug delivery, or a carrier in combination with nano targeting molecules, makes the PTX delivery system in the injection with larger area worth exploring, in order to reduce injection dosage forms to the pain of patients and inconvenience [12,13]. The non-injection form of paclitaxel in the treatment of ovarian cancer is mainly oral administration, so this article only introduces the research progress of oral administration.

At present, the main types of PTX Preparations for oral administration studies for ovarian cancer treatment and overcoming multidrug resistance include PTX-loaded polymeric micelles, Nanocrystals, SLNs, etc. (Table.1) [12,13].

Table 1. PTX Preparations for oral administration

PTX Preparations for oral administration			
Type of pharmaceutical preparation	Functional auxiliary material	Function	Characteristic
PTX-loaded polymeric micelles	CMCS-Qu-Polymeric-micelles (CM pqs)	Carrier, P-gp inhibitor	Increase mucosal adsorption, promote intestinal absorption, inhibit P-gp channel, avoid PTX efflux, and improve oral bioavailability
	PF127-CS/PF127-cysteine/nac micelles	P-gp inhibitor	Improve drug loading capacity and bioavailability
PTX nanocrystals	P1-g-CH	Stabilizer	Improve the dissolution rate of drugs and bioavailability
PTX solid lipid nanoparticles	SA-R8-PTX- SLN	Carrier	Promote the intestinal absorption of nanoparticles and overcome the efflux effect of P-gp on PTX
PTX solid dispersion	PVP-K30 and SLS	Carrier	Increase drug dissolution efficiency, high stability
PTX-loaded nps	PTX EMNP	Carrier	Improved intestinal absorption of PTX by osmosis
	TMC-PTX nps	Carrier	Improved intestinal absorption of PTX by osmosis
	FA-TMC-PTX nps	Carrier	Increase mucous membrane adsorption, promote intestinal absorption, selectivity
Miscellaneous formulations for oral administration	Hydrogel	Carrier	Low drug loading efficiency
	Telodendrimer micelle nanocarrier	Carrier	High cytotoxicity
	Clathrate	Carrier	High concentration of cyclodextrin can prevent clathrate precipitation, but it will produce hemolytic effect

6.1. Oral administration system

Oral preparations are ubiquitous, portable, easy to store, and painless to take, making them the preferred dosage form for most patients. However, there are some limitations. Firstly, sufficient doses are needed to achieve an effective therapeutic concentration. Secondly, need to have good absorption in the gastrointestinal tract, cannot stimulate the gastrointestinal tract; Moreover, easy to swallow, good smell and other requirements are also required control conditions.

The low solubility of PTX is the main reason for its poor oral absorption and low bioavailability. PTX has a high affinity with p-glycoprotein (P-gp) and other drug efflux pumps, which is another reason for the low oral bioavailability of PTX, and also a breakthrough points to overcome drug resistance [12]. Nanoparticle nanotechnology applied to PTX chemotherapy drugs can overcome drug resistance by inhibiting the function of various mechanisms such as efflux transporters on cell membranes [11]. Nanocarriers (nanoparticles, polymer micelles, liposomes, etc.) can help insoluble PTX to be dissolved, trapped, encapsulated or attached to the surface or interior of the carrier to reach the drug site smoothly, avoiding the addition of Cremophor EL and ethanol, and providing a more flexible delivery mode and formulation choice for drug delivery route [13].

6.1.1. PTX-loaded polymeric micelles

Polymer micelles consist of a central hydrophobic core and hydrophilic shell. The polymer micelles with hydrophilic shell extended the circulation time of PTX in vivo by avoiding the absorption of reticuloendothelial system. It also promoted the penetration and endocytosis of ovarian cancer cells and hindered the targeting of normal cells. Micelles can also deliver water-insoluble chemotherapeutic drugs and inhibit drug resistance through EPR effects, active internalization, endosomal triggered release, and drug escape. If PTX is encapsulated in the inner core, the hydrophilic shell not only increases solubility but also prevents enzymatic degradation of PTX in the gastrointestinal tract. The carrier materials of polymer micelles, such as chitosan, have good biocompatibility and can be degraded in vivo [15].

A carboxymethyl chitosan-quercetin conjugate polymer micelle (CQ PMs) with amphiphilic properties has been designed to encapsulate PTX (PTX-Loaded CQ PMs). Carboxymethyl chitosan (CMCS) as the hydrophilic block of polymer micelles can enhance drug absorption in the following ways:

- 1) the mucosal adhesion of CMCS can increase the retention time of PTX in intestinal mucosa.
- 2) CMCS reversibly open the tight junctions between small intestinal epithelial cells, allowing PTX to enter the human circulation through the paracellular pathway.
- 3) Quercetin as a hydrophobic block can inhibit the P-gp channel of OVCAR, avoid PTX efflux, and reduce the drug resistance of OVCAR.

It was found that PTX-loaded CQ PMs had sustained release characteristics in acid environment. Pharmacokinetic studies showed that PTX-Loaded CQ PMs significantly improved the oral bioavailability of PTX and showed better cytotoxicity and antitumor performance compared with Taxel®. Therefore, PTX-Loaded CQ PMs has the advantages of good stability, good sustained release characteristics, good oral availability, high anti-tumor efficacy and low cytotoxicity, which makes it an ideal carrier for PTX oral administration [13].

There is also a PF127-CS/PF127-cysteine/NaC micelles, which consists of Pluronic F127-chitosan, Pluronic F127-cysteine and sodium cholate. The micelles enhanced the oral availability of PTX, and Pluronic, as a P-gp inhibitor, enhanced PTX absorption [13].

6.1.2. PTX nanocrystals

Nanocrystals (NCs), also known as nanosuspensions, are stabilized by drug stabilizer. The solubility of PTX particles was increased by shrinking them to nanometer size and increasing the specific surface area of PTX. A stabilizer that improves nanostability, such as TPGS, can also inhibit P-gp-mediated PTX efflux. PTX nanocrystals (PTX/NCs) were prepared using Pluronic127 grafted chitosan (P1-g-CH) as a stabilizer. In this stabilizer, chitosan not only provides steric hindrance and electrostatic stabilization, but also promotes PTX uptake by cell bypass to avoid P-gp-mediated effusion [13].

6.1.3. PTX solid dispersion

Solid dispersants can make the drug highly dispersed in the carrier as a microcrystal, molecule, or amorphous state, thus increasing the available surface area for drug dissolution [13]. An oral solid dispersant of PTX prepared with PVP-K30 and SLS has similar pharmacokinetic properties, excellent

stability, and good taste to PTX premixed solutions containing polyoxyethyl castor oil and ethanol premixed solutions. However, this dosage form cannot target the tumor tissue after PTX enters the systemic circulation.

6.1.4. PTX solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are composed of physiologically and biocompatible lipids that can be degraded in vivo [11]. Octa-arginine (R8) is a classical cationic oligomeric membrane penetrating peptide, which is covalently linked to stearic acid-octaarginine (SA) to form an amphiphilic molecule, and incubates the PTX solid lipid carrier (PTX-SLN) with SA-R8. Stearic acid-Octaarginine modified solid lipid carrier containing paclitaxel (SA-R8-PTX-SLN) was obtained. Sa-r8-ptx-sln basically overcomes the efflux effect of P-gp on PTX. A study to determine the effect of PTX-encapsulated SLNs found similar cytotoxicity to conventional PTX injections in OVCAR-3 cells, suggesting that the SLNs-based route of administration is effective [12].

6.1.5. PTX-loaded NPs

Erythrocyte membrane is an endogenous component that can be used to deliver drugs. An erythrocyte membrane nanoparticle (EMNP) was designed to improve the penetration of PTX by intestinal absorption. Erythrocyte membrane is biocompatible and immunogenic, and PTX EMNP also shows sustained release characteristics. In addition to endogenous components, some biocompatible polymers such as chitosan and hyaluronic acid can also be used to deliver insoluble drugs. For example, PTX conjugated trimethyl chitosan nanoparticles (TMC-PTX NPs), used for oral administration of PTX, significantly increased intestinal permeability and significantly reduced ovarian tumor volume and improved survival compared with intravenous administration. Active targeting can also be achieved by modification with targeted molecules such as folic acid (FA-TMC-PTX NPs) to further improve the anti-tumor efficiency [13]. For folate receptor targeted therapy, a folate-containing PBM-NPs coated with natural compounds RES and docetaxel (DTX) has a good therapeutic effect in the treatment of prostate cancer, proving that this vector has a high potential to selectively target cancer cells. If applied to Ovarian cancer cells, it may be effective in drug resistant cancer [11].

6.1.6. Miscellaneous formulations for oral administration

Some other oral formulations of PTX, such as hydrogel [14], Dendrimers [11], clathrate, etc. Studies have found that low drug loading efficiency is the reason that limits the application of hydrogels [14]. The toxicity of dendrimers is difficult to be attenuated. Increasing the concentration of cyclodextrin can prevent precipitation of inclusion complexes, but high concentration of cyclodextrin will produce hemolytic effect.

A linear-dendritic Telodendrimer Micelle (TM) Nanocarrier to analyze the synergistic effects of two chemotherapeutic drugs (cisplatin and PTX), encapsulation of which exhibited high cytotoxicity against SKOV-3 OvCa Cells, also showed synergistic effects. Overall, dendrimers are promising drug delivery nanocarriers, with research efforts aimed at avoiding cytotoxicity and facilitating translation into clinical applications [11, 15].

7. Clinical problems of Paclitaxel

The injection of Paclitaxel has a wide range of applications in the treatment of ovarian cancer, has the characteristics of high efficiency and the mechanism of action is unique, with the continuous deepening of clinical research, a series of adverse reactions in the treatment of tumors with Paclitaxel injection has been found. Common adverse reactions including muscle pain, joint pain, bone marrow suppression, neurotoxicity, gastrointestinal reactions, allergic reactions. According to the experiment, all patients with malignant tumors under voluntary conditions and confirmed that there is no history of drug allergy are treated with paclitaxel injection, paclitaxel injection is added into saline or 5% glucose injection for intravenous infusion, the time is controlled at more than three hours, To prevent

severe allergic reactions, the patient before taking the drug take dexamethasone orally, or inject diphenhydramine if necessary, observing the adverse reactions of patients after the physical examination weekly, the results found that in 60 patients, The probability of myelosuppression is higher than the probability of hair loss higher than the probability of gastrointestinal reactions than the probability of limb numbness, the probability of these four items are all higher than 50%, the probability of myelosuppression and hair loss is even as high as 90%, and the overall experimental results are as follows Table.2 (The reaction level is divided according to the toxicity level of WHO anti-cancer drugs).

Table 2. Overall experimental results

Adverse reactions	I	II	III	IV	The probability(%)
Myelosuppression	19	15	21	4	98.33
Gastrointestinal reactions	16	12	9	0	61.67
Hair loss	22	19	13	0	90
Numbness in the extremities	21	11	0	0	53.33
Allergic reactions	1	1	0	0	3.33
Cardiac toxicity	2	1	0	0	5.00
Hepatotoxicity	3	1	0	0	6.67
Muscle pain and joint pain	5	1	1	0	11.67
Diseases of the blood system	3	2	0	0	8.33

Although paclitaxel is a natural drug, it still has many adverse reactions in clinical use. The reason for myelosuppression is the decrease in the activity of blood cell precursors. Lots of chemical drugs can cause myelosuppression, the only difference is the degree of myelosuppression. Under normal circumstances, the proliferation, maturation and release of cells in the bone marrow are relatively constant with the senescence, death, and excretion of granulocytes in the peripheral blood. Some tumors disrupt this balance during their treatment, with leukopenia or even pancytopenia, and this is the mechanism of myelosuppression. The reason for hair loss is that the hair follicle cells are indiscriminately attacked. Intracellular retention of paclitaxel may be a factor in the efficacy of the drug, but is also responsible for side effects such as peripheral neuropathy and hair loss [16]. To solve this problem, reduce the temperature of the head and thus reduce the blood circulation is widely used. Besides estrogen decline is a risk factor for paclitaxel-induced peripheral neuropathy. Paclitaxel, a microtubule-stabilizing agent, is useful to treat a wide range of cancers including breast, gastric, ovarian and uterine cancers, whereas it frequently causes peripheral neuropathy. Paclitaxel-induced peripheral neuropathy (PIPN) develops within weeks or months after the initiation of the chemotherapy in a dose-dependent manner, and may last from months to years after the chemotherapy completion [17].

8. Combination medicine

An effective way to solve the clinical problems of paclitaxel is to use combination drugs, which can reduce the side effects of paclitaxel by combining with other drugs. In current ovarian cancer treatment, paclitaxel is used in combination with cisplatin (or carboplatin) as a first-line drug and as a second-line drug in a dose-dense regimen after recurrence. Chemotherapy can significantly improve the symptoms of patients, but due to the high toxicity and side effects of chemotherapy drugs, ovarian cancer is prone to recurrence and multidrug resistance, which often leads to treatment failure [18]. Combining natural medicines is another option, which has the characteristics of high efficiency, low toxicity and low price. For example, Praeruptorin A is the main element of peucedanum praeruptorum dunn. It has potential therapeutic effects on a variety of tumors. In a preliminary drug screening trial, the researchers found that low concentrations of PA significantly enhanced the effect of paclitaxel on viability inhibition of A2780-paclitaxel-resistant strain. Based on this, in this study, ovarian cancer was cultured in vitro. A2780/TAX cells were used as the object to study the effect of PA combined

with paclitaxel on the viability, proliferation, apoptosis and migration of ovarian cancer cells, which is in order to explore developing low-toxicity and high-efficiency chemotherapy sensitizers for ovarian cancer, providing new ideas for improving the therapeutic effect of ovarian cancer. In general, by reducing the dose of paclitaxel when combined with PA, the adverse reactions of paclitaxel in clinical can be effectively reduced and provide patients with a more comfortable treatment process.

9. Conclusion

By analyzing the synthesis, application and clinical effect of Taxol, this paper found that the synthesis of Taxol still needs to be improved. Firstly, the natural extraction depends on the more advanced bacterial culture method to increase the yield, and in the case of artificial synthesis, there is now a synthetic method of high conversion rate, but it still needs to simplify the whole synthesis step, and then increase the yield. At the same time, the introduction of nanocarrier materials into traditional injections can significantly increase the water solubility of PTX, but prolonged intravenous infusion inevitably leads to poor patient compliance and is expensive. Oral preparations are widely available, which can reduce the inconvenience of injections. Oral preparations such as polymeric micelles, SLNs, Nanocrystals, etc. combined with P-gp inhibitors can improve the water solubility and bioavailability of PTX on the one hand, and reduce the drug resistance of OvCa cells on the other hand. Moreover, paclitaxel injection has a series of side effects such as myelosuppression, gastrointestinal reactions, and hair loss during the treatment of tumors. Most of the previous treatments were combined paclitaxel with Cisplatin or Carboplatin as a method for the treatment of ovarian cancer. If combined with natural medicines, the adverse reactions of the treatment process can be reduced by the reduce of the dose of paclitaxel and the drug Interaction.

Through this study, it can be found that the application of paclitaxel in ovarian cancer is considerable. This provides guidance for the improvement of paclitaxel application in the future. As long as the synthetic yield of paclitaxel can be optimized from the economic point of view, patients can take advantage of better ingestion to use the drug and the side effects can be reduced by the combination of drugs, the universal treatment of paclitaxel for ovarian cancer can be achieved.

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