# Exploration and Outlook of Recent Applications of Paclitaxel in Breast Cancer Treatment

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**Abstract.** Breast cancer, as the most common malignancy in women worldwide, compels enormous efforts in therapeutic research. Paclitaxel, a microtubule stabiliser, has shown its versatility and efficacy in treating various breast cancer subtypes. However, its use is often associated with dose-dependent toxicity and tumour cell resistance. Recent advances in nanotechnology have opened new avenues for delivering paclitaxel, offering potential solutions to these problems. This study aims to summarise paclitaxel's latest applications and prospects in breast cancer treatment, focusing on nanoformulations. The research methods include reviewing and analyzing the latest data from preclinical testing of nano-paclitaxel formulations and their evaluation in clinical practice. In addition, paclitaxel's mechanism of action, clinical application, main side effects, and development of its nano-formulations are also extensively discussed. This paper thoroughly summarises the present condition and prospects of using paclitaxel for treating breast cancer, especially nanoformulations. It also highlights the need for continued research and development to improve the efficacy of paclitaxel and reduce its consequences to serve breast cancer patients better.

**Keywords:** Breast Cancer, Paclitaxel, Nanoformulations.

## 1. Introduction

Breast cancer is the most prevalent cancerous growth among women globally. According to the 2020 figures, breast cancer has the highest cancer detection rate globally. This disease has been confirmed in 7.8 million women in the past half-decade. For 2020 alone, breast cancer accounted for nearly 12% of all new cancer cases worldwide, with roughly 2.26 million females receiving a breast cancer diagnosis and over 680,000 lives claimed [1]. Its incidence and mortality rates have steadily increased over the past decades, making it one of the significant threats to women's health worldwide.

With the advancement of science and technology, breast cancer treatment is becoming more and more refined and individualized, such as molecular targeted therapy and immunotherapy, which have been widely researched and applied in the new years. As new therapies are being used in clinics, scientists find that treatments that only target one cell will eventually face tumour resistance because of the unstable and varying genetics of tumour cells. Furthermore, the potential for severe toxicity in immunotherapy has garnered significant attention. It is widely accepted that the future of cancer treatment will likely involve a combination of traditional and innovative therapies. Certainly, broad-spectrum antitumor therapies, like chemotherapy, will continue to play a crucial and indispensable role in medical treatment.

Paclitaxel is a microtubule stabiliser that blocks mitosis in tumour cells by inhibiting the microtubule polymerization-depolymerization process, resulting in an antitumor effect. Chemotherapeutic agents like Paclitaxel (such as paclitaxel and docetaxel) and anthracyclines (like doxorubicin and epirubicin) are highly effective and commonly used in treating breast cancer, both in the adjuvant and metastatic stages. Therapeutic substances like paclitaxel (which encompasses docetaxel) and anthracyclines (comprising alternatives such as doxorubicin and epirubicin) are frequently administered for managing breast cancer, regardless of their supplemental or advanced phase. These agents are highly effective and widely utilized. However, some problems are associated with paclitaxel, such as dose-dependent toxicities and tumour cell resistance. In recent years, with nanotechnology’s application in drug delivery, nanocarrier systems have become an effective way to solve the problem of toxic side effects of paclitaxel [2].

Therefore, this article summarises current breast cancer research focusing on paclitaxel. This report provides an overview of the current status of using nano-paclitaxel formulations in treating breast cancer. The information is based on the most recent data gathered from preclinical testing of these formulations and their evaluation in clinical practice.

## 2. Pharmacological effects of paclitaxel

Paclitaxel is frequently utilized in cancer treatment, where it works by blocking the polymerisation of microtubules as part of its pharmacological mechanism of action. Microtubules are essential intracellular structures involved in cell division, cellular transport, and maintenance of the cytoskeleton [3]. Paclitaxel stabilises the structure of microtubules by binding to microtubules and promoting the assembly of microtubule protein subunits, thus preventing the division and growth of cancer cells.

Specifically, paclitaxel binds to microtubulin subunits α and β, decreasing the critical concentration of microtubulin and promoting the lengthening of microtubulin polymers. This causes microtubules to become more stable and interferes with microtubule dynamics. The role of microtubules in cell division is crucial, and paclitaxel's effect is to stop cell division in either the G2 or M phase [4]. In addition, paclitaxel interferes with the kinetics of microtubules and microtubule polymerisation, retarding mitotic progression by inducing the failure of chromosome segregation, ultimately leading to apoptosis and mitotic arrest.

The mechanism of action of paclitaxel is also associated with regulating calcium signals. By triggering the opening of portable mitochondrial pores (PTP) reduces the amount of calcium ions stored in nerve cells. The remaining calcium ions release deflator factor C (cytochrome c) from the mitochondria into the cytoplasm and thus begin to reverse. In addition, paclitaxel can also trigger apoptosis by binding to extracellular calcium reservoirs and inducing the inward flow of intracellular calcium ions [5]. This regulation of calcium signalling has essential implications for anti-mitotic drugs' side effects and cytotoxicity.

Paclitaxel has been discovered to influence the levels of microRNAs, tiny RNA molecules that aren't coded into protein but play a critical role in managing how genes are expressed. Moreover, paclitaxel also contributes to the regulation of microtubule and calcium signalling. Studies have found that paclitaxel application can alter the expression levels of specific miRNAs in tumour cells that may have tumour suppressor potential [6]. This suggests that by regulating miRNA expression, paclitaxel may affect cancer cell growth and metastasis.

Moreover, paclitaxel possesses immunomodulatory properties. It can stimulate macrophage activity and foster the production of immune system messengers, including molecules like TNF-α and IL-12. This, in turn, activates defense cells that amplify the host’s immune response and remove cancerous cells [7]. Furthermore, paclitaxel can promote the maturation of antigen-presenting cells and enhance the immune response [8].

To summarize, paclitaxel acts as an anticancer medication by hindering the advancement of cancerous cells and triggering cell death through diverse mechanisms., such as blocking the polymerisation of microtubules, regulating calcium signalling, and affecting miRNA expression profiles and immune regulation. These studies provide an essential theoretical basis for our in-depth understanding of the pharmacological effects of paclitaxel and guidance for further development and optimisation of anticancer therapeutic strategies of paclitaxel and its derivatives.

## 3. Paclitaxel in Breast Cancer

Breast cancer is a widespread illness that affects women across the globe and is notorious for its malignant characteristics [9]. Its incidence and mortality rates are the highest among female malignant tumours. Breast cancer is classified based on the biological traits of the tumour, such as the condition of Hormone Receptors, the state of Human Epidermal Growth Factor Receptor 2, and

the level of proliferation index Ki-67 presentation. Based on these characteristics, breast cancer can be classified into three subtypes: Hormone Receptor +/- HER2-, HER2+, and Triple-Negative [10].

### 3.1. Hormone receptor-positive breast cancer

The most prevalent form of breast cancer is HR+/HER2-, making up around 70% of all cases [10]. Many hormone receptors on the cell surface characterise these tumours. Endocrine therapy (ET) is the primary standard treatment, but developing resistance to ET is almost inevitable. Patients resistant to endocrine therapy can be treated with targeted therapeutic agents, such as paclitaxel in combination with a CDK4/6 inhibitor (abemaciclib), as an effective alternative treatment [11]. Paclitaxel has shown significant efficacy in treating hormone receptor-positive breast cancer, especially when combined with other agents. For example, a study of a neoadjuvant chemotherapy regimen using an anthracycline in combination with paclitaxel showed a doubling of pathologic complete remission (pCR) compared to the anthracycline regimen alone [12]. In addition, with immunotherapy, paclitaxel is mainly used with monoclonal antibodies. For example, the combination of vantictumab (an anti-frizzled antibody) and paclitaxel has shown efficacy in treating HER2-negative breast cancer and has been well tolerated [13]. Miles D conducted a phase III clinical trial that showed the addition of bevacizumab to paclitaxel significantly improved the treatment of HER2-negative metastatic breast cancer (mBC), leading to better progression-free survival [14].

### 3.2. HER2-Positive Breast Cancer

According to statistics, about one in five breast tumours are classified as HER2 positive [10]. This means there are a significant number of HER2 receptors on the surface of the tumour cells. This type of breast cancer is typically treated with chemotherapy and HER2-targeted antibodies or small molecule inhibitors. Paclitaxel, as a first-line agent in a chemotherapy regimen, combined with lapatinib and trastuzumab, displays an outstanding treatment response in BC exhibiting HER2 positivity. When used with capecitabine, it was more effective in treating patients with advanced HER2 cancer [15]. According to the latest study, the combination of paclitaxel and trastuzumab significantly improves survival in patients with HER2-positive. A study covering more than 1,000 patients with HER2-positive breast cancer found that the three-year disease-free survival rate of patients treated with paclitaxel in combination with trastuzumab was 15 percentage points higher than that of patients using trastuzumab alone [16].

### 3.3. Triple-Negative Breast Cancer

TNBC is a particular kind of breast cancer that makes up 10-15% of all breast cancer cases. Compared to the other two subtypes, Triple-Negative breast cancer is more likely to recur and is more common in younger female cohorts. As detected through immunohistochemistry, TNBC is characterised by the absence of estrogen receptors, progesterone receptors, and HER2 [10]. The most common scientific treatment for TNBC is surgical removal, radiotherapy, and chemotherapy using paclitaxel, anthracyclines, and alkylatinFurthermoreg agents, as few specific receptors are available for targeting. Additionally, given the high degree of invasiveness and metastasis of patients with advanced TNBC, obtaining favourable results with targeted or hormonal treatment alone is challenging. In clinical trials conducted in recent years, paclitaxel is more frequently seen in combination with PD1/PD-L1 antibodies, such as phase I- III clinical with Pembrolizumab, atezolizumab, durvalumab, etc [17]. To varying degrees, these clinical studies have affirmed the potential of combining paclitaxel and monoclonal antibodies in treating TNBC. Recent studies have found that exchanging paclitaxel for nano-paclitaxel with monoclonal antibodies improves PCR rates and DFS [18]. When Atezolizumab and albumin-conjugated paclitaxel are used together, it can extend the time before the progression of metastatic TNBC in patients, particularly those who have high PD-L1 expression [19].

According to clinical trial results, combination therapy can extend patients' median overall survival (OS) by nearly ten months in PD-L1-positive, unresectable TNBC cases. The FDA has approved

atezolizumab in combination with the chemotherapy drug nab-paclitaxel for treating this condition [17].

Overall, paclitaxel is essential in treating all types of breast cancer. The chemotherapeutic agent paclitaxel has shown significant efficacy for all three subtypes, especially when combined with other treatments. In the most common HR+/HER2- breast cancer type, paclitaxel can be an effective alternative for patients resistant to endocrine therapy. In HER2+ breast cancer, combinations of paclitaxel with targeted antibodies or small molecule inhibitors have produced encouraging outcomes for enhancing survival. Recent trials have emphasised the potential of combining paclitaxel with PD1/PD-L1 antibodies for the more aggressive triple-negative subtype. Together, these findings underscore the versatility and efficacy of paclitaxel in treating different breast cancer subtypes, emphasising its pivotal role in the evolving field of breast cancer treatment.

## 4. Adverse effects of paclitaxel

The main side effects of paclitaxel in treating breast cancer include hypersensitivity reactions and neuropathy. Due to the poor solubility of paclitaxel, IV solutions of paclitaxel are obtained using Cremophor EL and ethanol dissolved in Taxol preparations, but Cremophor EL and ethanol can also cause serious side effects for patients such as hypersensitivity reactions and sensory neuropathy. Taking paclitaxel usually causes an allergic reaction within a short time. These reactions include difficulty breathing, wheezing, hives, skin flushing, rash, low blood pressure, and swelling due to fluid buildup. In addition, allergic reactions to paclitaxel usually stop treatment immediately. However, allergic reactions may be lessened by taking dexamethasone, phenelzine, or tagamet before surgery. It is worth noting that peripheral neuropathy after administration was found to be related to the dose of paclitaxel. In the test, reducing the dosage of paclitaxel by one-fifth or giving a certain amount of amitriptyline could reduce the adverse reactions related to the nervous system. Moreover, patients who took paclitaxel more frequently were more likely to have symptoms of neuropathy of varying degrees [10].

Adverse impacts such as a decrease in neutrophils, fever-accompanied neutropenia, and occurrences of infections have been noted among those undergoing treatment with paclitaxel, but the most common remains neuropathy. To date, the exact mechanism by which paclitaxel causes neuropathy is unknown, but recent clinical studies have found that pregabalin and duloxetine are well-tolerated and effective in targeting the relief of neuropathic pain induced by paclitaxel chemotherapy. Still, duloxetine is not as efficacious as pregabalin at the same dose [20]. Ethosuximide and alpha-lipoic acid have also shown efficacy and value in targeting neuropathic symptoms following paclitaxel chemotherapy [10,21].

Overall, using paclitaxel in breast cancer treatment can lead to significant survival improvements, but its adverse effects may lead to treatment interruptions and compromise outcomes. Therefore, in-depth studies of the mechanisms of paclitaxel and its adverse effects are essential for better-managing breast cancer patients.

## 5. Nanopaclitaxel in Breast Cancer

Although there are other forms of paclitaxel, such as oral formulations, injections, etc., nanoformulations are more promising in breast cancer treatment due to their advantages in solubility and safety. Nano-formulations can improve the therapeutic effect and reduce side effects by improving the way of drug absorption and release by utilising the EPR effect, which is especially important in the treatment. Chemotherapy, as the first-line therapy for the treatment of breast cancer, requires long-term use of paclitaxel, alkylating agents, and doxorubicin, which often cause serious side effects.

Since 2004, PTX nano-formulations, like Lipusu, Abraxane, and Genexol-PM, have been developed to reduce the toxicity of solvents and doses. These nanocarriers connected by non-covalent

interactions have not achieved the expected curative effect in clinical treatment because they cannot guarantee the effective delivery of drugs to tumours. However, these traditional nanoscale paclitaxel preparations have propelled the progress of clinical studies and the use of paclitaxel.

In recent years, new nanocarriers have been developed based on traditional nanocarriers with more advantages in drug loading rate, stability, targeting, and safety. For example, NK105 and NK012, both nano-paclitaxel formulations in clinical trials, have shown good antitumor activity and low toxicity by using polyamide (PAA) and polyethene glycol (PEG) to encapsulate paclitaxel. Also in clinical trials is Opaxio (polyethene glycolic paclitaxel), a nanocarrier that has shown advantages in drug solubility and stability through using polyethene glycol (PEG) as a carrier [22].

In addition, various combination therapies based on traditional nanomedicines and novel nanomedicines have also been used to treat breast cancer, and some results have been achieved. The clinical trials demonstrated that incorporating Abraxane alongside bevacizumab and capecitabine in managing HER2-negative advanced breast cancer yielded promising outcomes, enhancing patients' ORR and PFS [22]. Knowing that this treatment can also increase the likelihood of experiencing toxic side effects is important. Still, in any case, it also provides a new idea and direction for applying nano-paclitaxel preparations in breast cancer.

## 6. Conclusion

This article delves into the recent applications and perspectives of paclitaxel in breast cancer treatment. As an antitumor drug, paclitaxel's unique mechanism of action and remarkable efficacy occupy an essential position in BC treatment. We provide a detailed description of the pharmacological effects, clinical applications, and significant side effects of paclitaxel, as well as a review of the development of its nanoformulations in breast cancer treatment.

Despite the achievements of paclitaxel preparations in breast cancer treatment, some challenges in its clinical application, like side effects and control of drug resistance not mentioned in this paper. These issues need to be explored more deeply in our future studies. Meanwhile, we also see the potential of nano-paclitaxel formulation in breast cancer treatment, especially in emerging immunotherapy combination therapy.

Overall, using paclitaxel in breast cancer treatment is a complex and in-depth topic that requires continuous research and exploration. Looking forward, the anticipation is for creating more potent versions of paclitaxel treatments to enhance therapeutic outcomes and lessen adverse reactions, thereby optimising care for those with breast cancer. We also look forward to the new application and development of nano-paclitaxel formulations in breast cancer treatment, which will open up a new path for breast cancer treatment.

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