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Review

Paclitaxel anti-cancer therapeutics: from discovery to clinical use

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ABSTRACT

Paclitaxel (PTX), a valuable natural product derived from *Taxus* species, exhibits remarkable anti-cancer properties. It penetrates nanopores in microtubule walls, interacting with tubulin on the lumen surface and disrupting microtubule dynamics, thereby inducing cytotoxic effects in cancer cells. PTX and its derivatives have gained approval for treating various diseases due to their low toxicity, high efficiency, and broad-spectrum application. The widespread success and expanding applications of PTX have led to increased demand, raising concerns about accessibility. Consequently, researchers globally have focused on developing alternative production methods and applying nanocarriers in PTX delivery systems to enhance bioavailability. This review examines the challenges and advancements in PTX sourcing, production, physicochemical properties, anti-cancer mechanisms, clinical applications, trials, and chemo-immunotherapy. It aims to provide a comprehensive reference for the rational development and effective utilization of PTX.

1. Introduction

Paclitaxel (PTX), also known as taxinol, is a diterpenoid compound belonging to the taxane family and is regarded as one of the most potent and commercially successful natural-product-derived anticancer agents. Marketed under the brand name taxol, paclitaxel has played a pivotal role in the treatment of advanced and refractory cancers. In 1992, taxol received approval from the United States Food and Drug Administration (FDA) for the treatment of advanced ovarian cancer. Since then, paclitaxel and its derivatives have been further approved for the treatment of a broad range of malignancies, including breast, lung, cervical, and pancreatic cancers, as well as Kaposi's sarcoma [1]. Due to its relatively mild side effects, PTX has become a widely used anti-cancer drug in clinical practice. Currently, PTX and several related taxane analogs [e.g., PTX injection, liposome, albumin-bound nanoparticles PTX (nab-PTX), polymeric micelles (PMs), oral solution, docetaxel injection, and cabazitaxel injection] have emerged as leading anti-cancer agents. According to recent statistics, the PTX market size was estimated at USD 424.41 million in 2023 and is projected to reach USD 466.21 million in 2024, with a compound annual growth rate (CAGR) of 9.92%, potentially reaching USD 822.92 million by 2030 [2].

PTX was initially extracted from the bark of the Pacific yew [*Taxus brevifolia* (*T. brevifolia*)] [3]. However, the bark of *Taxus* species contains PTX in low concentrations of 0.01%–0.05% [4], which is insufficient to meet market demand. Consequently, researchers worldwide have explored alternative methods for PTX production. Several approaches, including artificial cultivation of *Taxus* plants, microbial fermentation, total chemical synthesis, and tissue and cell culture, have been developed and implemented [4]. Presently, PTX production for medical use relies on semi-synthesis from 10-deacetylbaccatin III (10-DAB), a more abundant precursor isolated from *Taxus* needles, which serves as the starting material for chemical synthesis. Plant cell cultures derived from various *Taxus* species are also utilized for commercial PTX production [5]. Recently, the complete elucidation of the biosynthetic pathway for PTX [6] has paved the way for metabolic engineering and synthetic biology approaches to enhance PTX production in *Taxus* cell cultures or heterologous hosts, such as *Saccharomyces cerevisiae* (*S. cerevisiae*).

PTX appears as a white crystalline powder with extremely low water solubility. Its application in cancer therapy faces limitations due to several factors, including poor solubility, recrystallization upon dilution, rapid bloodstream clearance, non-specific distribution, and co-solvent-induced toxicity [7]. Consequently, there is an urgent need to investigate novel PTX formulations that exhibit low toxicity while maintaining or enhancing anti-tumor efficacy. The incorporation of nanotechnology into drug administration and delivery has markedly advanced modern medicine [8]. Nanocarriers, in particular, have demonstrated exceptional po-

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tential in developing innovative drug delivery systems, owing to their nanoscale dimensions, favorable physicochemical properties, and high surface-to-volume ratio [9]. Nanoparticle delivery systems can enhance the aqueous solubility of PTX and mitigate side effects by evading recognition by the reticuloendothelial system in healthy tissues [10]. Moreover, their small diameter (ranging from several to several hundred nanometers) amplifies the enhanced permeability and retention (EPR) effect, enabling preferential accumulation of PTX at tumor sites [11]. To date, PTX delivery systems based on polymeric, lipid, and inorganic nanoparticles, as well as deoxyribonucleic acid (DNA) nanostructures, nanosized graphene oxide, and carbon nanotubes, have been developed and garnered increasing attention in clinical applications [12].

This review explores recent developments in PTX research, emphasizing new insights into its origin, manufacturing processes, physicochemical characteristics, anti-cancer mechanisms, clinical applications, trials, and chemo-immunotherapy. Our objective is to offer a comprehensive reference for the rational development and efficient utilization of PTX in cancer treatment.

2. Discovery, natural distribution, and synthesis of PTX and derivatives

2.1. PTX resource from plants and fungi

PTX was initially extracted from the bark of the Pacific yew tree, *T. brevifolia*, in 1963 [3]. It was later discovered in the bark of other *Taxus* species, which remain the primary source of PTX to date. The *Taxus* genus comprises 13 recognized species and two additional cryptic species (identified as the Emei and Qinling types). These species are found in temperate and subtropical regions of the northern hemisphere and are considered "national treasures" by 42 countries, with the United Nations imposing logging bans [4, 13]. China hosts four officially recognized *Taxus* species and one additional variety: *Taxus chinensis* (*T. chinensis*), *Taxus mairei* (*T. mairei*), *Taxus wallichiana* (*T. wallavhiana*), *Taxus cuspidate* (*T. cuspidata*), and *Taxus yunnanensis* [14]. Notably, the dry leaves and twigs of *T. mairei* are utilized as traditional Chinese medicine in clinical applications in Hunan, Zhejiang, Jiangsu, and other provinces.

Certain fungi demonstrate the capability to biosynthesize PTX. In 1993, researchers identified PTX in the fungus *Taxomyces andreanae*, which inhabits the phloem (inner bark) of yew trees [15, 16]. This discovery, given the rapid growth and ease of cultivation of endophytic fungi, generated optimism for large-scale biotechnological production of fungal PTX. In recent years, the production of PTX from endophytic fungi has emerged as a viable method. Presently, approximately 200 endophytic fungi from both *Taxus* and non-*Taxus* species have been found to biosynthesize PTX, including *T. brevifolia*, *T. wallavhiana*, *T. mairei*, *T. chinensis*, *Taxus baccata* (*T. baccata*), and others [4, 17]. However, industrial utilization remains challenging due to the limited understanding of the PTX biosynthetic pathway. Further research is necessary to elucidate how transferring complete and complex biosynthetic pathways can facilitate PTX production in endophytic fungi, although the transfer of PTX biosynthesis genes and transcription factors is still in its early stages. Enhancing PTX-producing fungi through biotechnological methods and optimizing culture conditions could potentially increase yield, making industrial-scale PTX production from endophytic fungi feasible in the future.

The tissue and cell culture of *Taxus* species represents a viable method for PTX production. This approach was initially established in 1989 using suspension cell cultures of *T. brevifolia* to produce PTX [18]. Subsequently, other *Taxus* species, including *T. cuspidata*, *T. baccata*, *Taxus canadensis*, *Taxus floridana*, *T. wallichiana*, *Taxus globosa*, *Taxus media* (*T. media*), and *T. chinensis* have also demonstrated the ability to produce PTX and PTX-like compounds in high yields, with *T. chinensis* showing particular promise [4]. Kochkin et al. evaluated the callus and suspension cell cultures of three *Taxus* species (*T. baccata*, *T. canadensis*, and *T. wallichiana*) and two *Taxus* × *media* hybrids. Notably, 14-hydroxylated toxoids were isolated from the biomass of suspension cultures of *T. baccata* cells for the first time. Most of the investigated cell cultures maintained the ability to form PTX diterpenoids, regardless of species, cell line origin, or conditions. Under *in vitro* culture conditions, nonpolar 14-hydroxylated taxoids (in the form of polyesters) predominated in all cell lines, contrasting with the 13-OH taxoids found in plants [19]. The formation of 14-OH toxoids in cell cultures may be attributed to their lower toxicity to proliferating cells compared to 13-OH derivatives, given that PTX and its derivatives disrupt the cytoskeleton, which is lethal to most eukaryotic cells. Currently, PTX is obtained directly from suspension cultures of specific *Taxus* cell lines cultivated in fermentation tanks, yielding an extremely enriched powder containing approximately 40% PTX. Consequently, the use of *Taxus* plant cells for PTX production is a feasible method and is likely to play a significant role in the industrial-scale production of PTX in the future [20].

2.2. The biosynthesis pathway and heterologous biosynthesis of PTX

2.2.1. The biosynthesis pathway of PTX

PTX is a tetracyclic diterpenoid compound whose biosynthetic pathway has been progressively elucidated through the identification and cloning of its key enzymes in *Taxus* since 2000. The complete biosynthetic route was only recently established following the characterization of the final three previously unknown enzymes [5, 6]. The biosynthesis of PTX can be divided into three major stages (Fig. 1). The first stage involves the biosynthesis of taxadiene-5α-ol from geranylgeranyl diphosphate (GGPP), catalyzed by taxadiene synthase (TXS) [21] and taxane 5α hydroxylase (T5αH) [22]. GGPP, a common precursor of diterpenoid compounds, is formed by the condensation of one molecule of dimethylallyl pyrophosphate (DMAPP) and three molecules of isopentenyl pyrophosphate (IPP), catalyzed by geranylgeranyl diphosphate synthase (GGPPS). DMAPP and IPP are derived from the 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway in plastids and the mevalonate (MVA) pathway in the cytoplasm. The second stage involves the conversion of taxadiene-5α-ol into the tetracyclic core structure, baccatin III, through a series of oxidation and acylation reactions. Multiple cytochrome P450 monooxygenases catalyze hydroxylations at C5 [22], C2 [23], C7 [24], C10 [25], and C13 [26], while acyltransferases mediate the acylation at C5-OH [27], C10-OH [28], C2-OH [29], have been cloned and characterized in early studies. Recent advances, facilitated by the release of *Taxus* genome sequences [15, 30, 31], have led to the identification of additional enzymes, including taxane oxetanase 1 (TOT1) and TmCYP1, which catalyze the formation of the oxetane ester [6, 32], taxane 1β hydroxylase (T1βH) and taxane 9α hydroxylase (T9αH), which introduce hydroxyl groups at C1 and C9, respectively, and taxane 9α oxidase (T9αO), which mediates the oxidation at C9 [5]. The third stage focuses on side-chain biosynthesis and the final assembly of PTX. Phenylalanine aminomutase (PAM) [33] and phenylalanoyl CoA ligase (PCL) [34] are responsible for generating the side-chain precursors, which are attached to baccatin III by 3-amino-3-phenylpropanoyl transferase (BAPT) [35]. Final modifications include hydroxylation by 3'-*N*-debenzoyl-2'-deoxytaxol 2'α-hydroxylase (T2'αH) [23] and 3'-*N*-debenzoyl-2'deoxytaxol *N*-benzoyl transferase (DBTNBT) [36], ultimately yielding the active PTX molecule. It has been hypothesized that these fungi harbor bio-

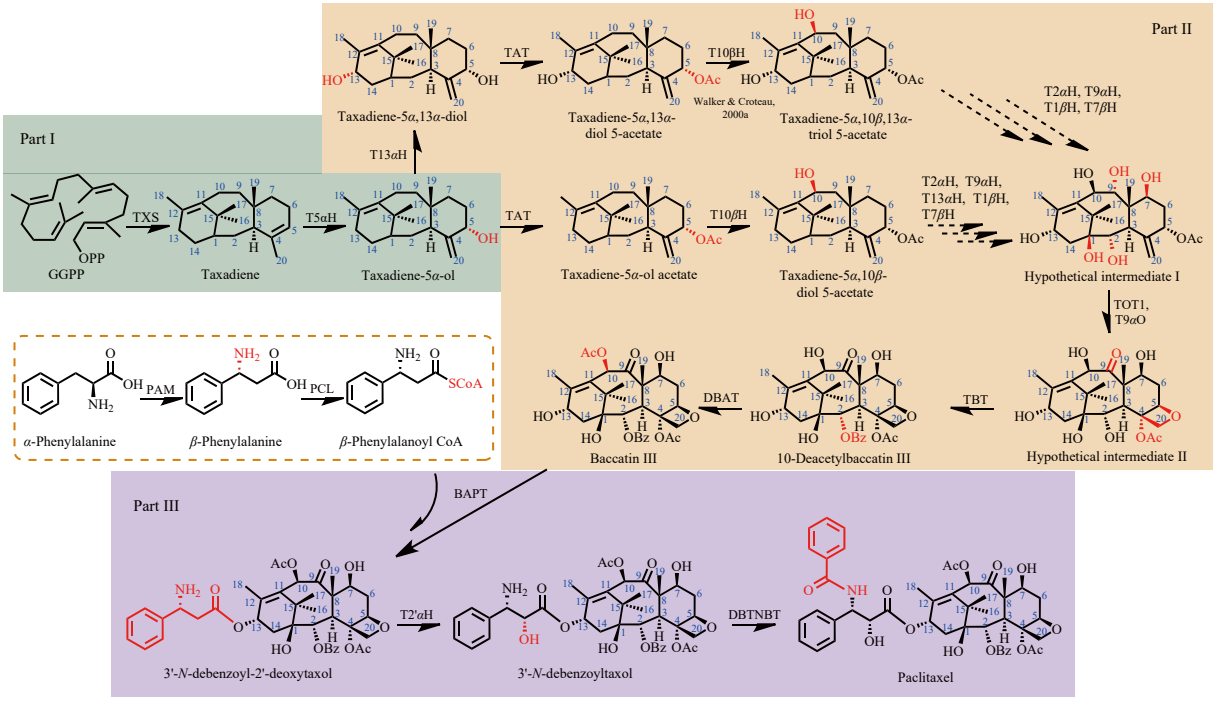

Fig. 1 The paclitaxel biosynthesis pathway in *Taxus*. All enzymes present here have been charactered and verified; dashed arrows represent undefined catalytic sequences of enzymes.

synthetic genes homologous to those found in *Taxus* [37], primarily based on PCR screening of similar sequences. However, conflicting evidence regarding PTX biosynthesis in fungi has been reported, and whether the biosynthetic pathway is truly conserved between *Taxus* and endophytic fungi remains an important question for future research [38].

PTX is one of the secondary metabolites in *Taxus*. Secondary metabolites in plants are typically concentrated in specific tissues or specialized organs rather than being uniformly distributed throughout the plant [39], indicating complex spatial control of their synthesis. The leaves of *Taxus* are the primary industrial source for PTX production. To elucidate the precise distribution, biosynthesis, and transcriptional regulation of PTX, researchers have employed MS imaging and single-cell sequencing to visualize the distribution of active metabolites and gene expression patterns in different cell types. MALDI-imaging MS revealed that taxoids such as 10-deacetylcephalomannine, 10-deacetylpaclitaxel, baccatin III, and 10-DAB predominantly accumulate in spongy mesophyll cells, while flavonoids like ginkgetin, quercetin, and rutin are mainly found in epidermal cells. Cell-type annotation demonstrated that most PTX biosynthesis genes are expressed predominantly in leaf mesophyll cells, whereas phenolic acid and flavonoid biosynthesis genes are highly expressed in the leaf epidermal cells. This suggests that PTX precursors are synthesized in the tissues where they ultimately accumulate. Furthermore, several novel, cell-specific transcription factors involved in secondary metabolite biosynthesis were identified, including MYB17, WRKY12, WRKY31, ERF13, and bHLH46 [40]. Transcription factors provide selective control over plant metabolism and serve as powerful tools for modifying plant metabolism [41]. For instance, *TcMYB29a* is highly expressed in the needles and roots. Overexpression of *TcMYB29a* in *T. chinensis* cell suspension cultures resulted in increased PTX accumulation and upregulated expression of PTX-biosynthesis-related genes, including *TXS*, *T5αH*, and *DBTNBT*, compared to controls [42]. Female *T. media* trees accumulate more PTX than male trees. TmMYB39, a female-specific MYB transcription factor, binds to the promoters of the *GGPPS*, *T10OH*, *T13OH*, and taxane 2*α*-*O*-benzoyl transferase (*TBT*) genes. Bimolecular fluorescence complementation and yeast two-hybrid assays revealed an interaction between TmMYB39 and TmbHLH13. The TmMYB39-TmbHLH13 complex transactivated the expression of *GGPPS* and *T10OH* genes, suggesting that TmMYB39 may regulate PTX biosynthesis through an MYB-bHLH module. This research provides a potential explanation for the sexually dimorphic biosynthesis of PTX in *T. media* [43]. To date, only a few transcription factors have been identified as playing significant roles in regulating genes in the PTX biosynthetic pathway. Other factors involved in hormone signaling positively regulate PTX biosynthesis, but the associated regulatory mechanisms remain unclear [44].

2.2.2. Heterologous biosynthesis of PTX

As researchers continue to elucidate the PTX biosynthesis pathway, efforts have been made to reconstruct the known biosynthetic pathway of PTX in various heterologous hosts, including *Escherichia coli*, yeast, and *Nicotiana benthamiana* (Fig. 2). These endeavors have resulted in the successful heterologous production of PTX and its analogs, such as taxadiene, taxadien-5α-ol, oxygenated taxanes, and baccatin III. Nevertheless, achieving industrial-scale heterologous production of PTX with competitive advantages still necessitates extensive experimentation and optimization.

(1) Biosynthesis of PTX in prokaryotic cell chassis

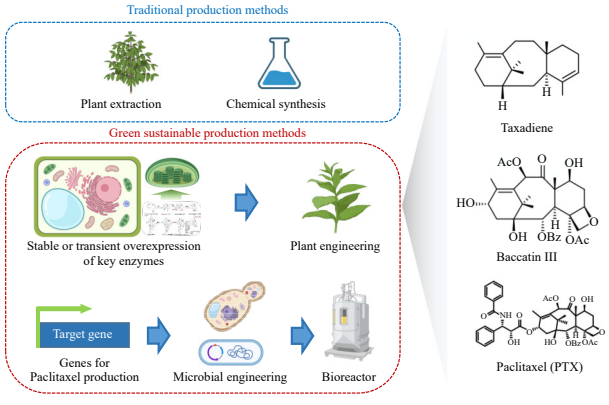

Fig. 2 Heterologous synthesis of PTX-related metabolite.

A significant advancement was the successful enhancement of taxadiene production in an engineered *E. coli* strain, achieving a titer of approximately 1 g·L^{-1}, the highest reported to date [45]. Recent research has concentrated on screening key enzymes, such as TXS and cytochrome P450 reductase (CPR), involved in the pathway. Furthermore, optimizing the linker for the fusion of taxadiene-5*α*-hydroxylase with its reductase partner CYP, coupled with improved fermentation conditions, resulted in an increase in the titer of oxygenated taxanes to 27 mg·L^{-1} and taxadien-5α-ol to 7 mg·L^{-1}, representing approximately 12-fold and 23-fold increases, respectively, compared to the parent strains [46]. However, expressing CYP enzymes in prokaryotic cells, such as *E. coli*, presents challenges due to the absence of an endomembrane system and the hydrophobic *N*-terminus of CYP enzymes, which can reduce solubility and impede functional expression. Consequently, there are inherent limitations to utilizing *E. coli* and other prokaryotic cells as heterologous production systems for PTX, necessitating further research to overcome these obstacles. Recent studies have attempted to establish partial heterologous PTX biosynthesis in cyanobacteria, achieving the conversion of carbon dioxide into taxadiene-5*α*-ol of 4.32 mg·L^{-1}, providing a theoretical foundation for expanding the use of photosynthetic bacteria as cell factories [47].

(2) Biosynthesis of PTX in yeast chassis

Establishing a co-culture system that leverages the complementary advantages of different hosts effectively addresses the respective limitations of each organism. Metabolic intermediates produced by *E. coli* were utilized by *S. cerevisiae*, enabling stable co-culture in a single bioreactor and yielding 33 mg·L^{-1} of oxygenated taxanes [48]. Several strategies were implemented to further enhance yields in *S. cerevisiae*. Initially, the low expression and solubility of TXS were identified as critical bottlenecks. By fusing TXS with fusion protein tags for multicopy chromosome integration, the taxadiene titer was increased 22-fold at 30 °C. Additionally, TXS performance was observed to be temperature-dependent, with a maximum taxadiene titer of 129 mg·L^{-1} at 20 °C [49]. Building on these findings, the incorporation of sequences encoding CYP725A4, CPR, and taxadiene-5*α*-ol-*O*-acetyl transferase (TAT) from *T. cuspidata* resulted in taxadiene-5*α*-ol isomer levels of approximately 20 mg·L^{-1}, and the total oxygenated taxane content increased 2.7-fold to 78 mg·L^{-1} [50]. Further optimization of culture conditions using nutrient-limited micro-mediums for taxane accumulation yielded 387 mg·L^{-1} [51]. Following the elucidation of the oxetane synthesis process, an engineered *S. cerevisiae* strain co-expressing 12 pathway genes successfully converted taxadiene-5*α*-ol into the precursor of baccatin III, 1*β*-dehydroxybaccatin VI [52]. In addition to *S. cerevisiae*, taxadiene biosynthesis has also been achieved in the oleaginous yeast *Yarrowia lipolytica* [53]. By exploiting the endogenous MVA pathway, enhancing the soluble expression of TXS, and employing a push-pull strategy to increase precursor supply and reduce bypass metabolism, a taxadiene yield of 101.4 mg·L^{-1} was achieved following fed-batch fermentation.

(3) Biosynthesis of PTX in plant chassis

In comparison to microbial systems, plant chassis offer considerable advantages for membrane protein expression, precursor supply, product tolerance, and compartmentalized synthesis. This is especially relevant for PTX synthesis, which requires the catalytic activity of multiple CYP enzymes. The expression efficiency of CYPs is generally low in microorganisms. A chloroplast-based metabolic engineering approach, coupled with enhanced isoprenoid precursors, yielded 56.6 μg·g^{-1} of taxadiene and 1.3 μg·g^{-1} of taxadiene-5*α*-ol, highlighting tobacco's potential as an alternative platform for PTX production [54]. Chloroplast compartmentalized engineering proves to be an effective method for PTX production. By introducing a truncated version of TXS from *T. brevifolia* (without the transit peptide coding sequence) into the tobacco chloroplast genome, transgenic tobacco leaves achieved a taxadiene yield of 87.8 μg·g^{-1} [55].

In 2023, researchers utilized transcriptomics, cell biology, metabolomics, and pathway reconstruction to identify the complete gene set necessary for PTX production. The biosynthetic pathway was successfully reconstructed in *N. benthamiana*, yielding approximately 100 μg·g^{-1} (fresh weight) taxadiene for baccatin III biosynthesis *via* 13 genes. They also achieved the synthesis of baccatin III to PTX [5]. Reducing the expression of taxane 15*α* hydroxylase (T15*α*OH) in tobacco can more effectively direct the metabolic flow to the key intermediate taxadiene-5*α*-ol, potentially enhancing PTX yield [56]. Recently, a streamlined baccatin III synthesis pathway (9 genes) was discovered. By transiently expressing *TOT* and *T9αH-1*, along with seven known synthetic genes, including *TXS*, *T5αOH*, taxane 13*α* hydroxylase (*T13αOH*), taxane 2*α* hydroxylase (*T2αOH*), taxane 7*β* hydroxylase (*T7βOH*), *TAT*, and *TBT*), researchers successfully produced baccatin III in *N. benthamiana* [6].

2.3. The chemical synthesis of PTX

2.3.1. Commercial production of PTX

From the 1960s to the 1980s, PTX was obtainable only in low yields through isolation from the bark of the Pacific yew. In 1981, French scientist Potier discovered a compound containing the PTX skeleton, 10-DAB, in the needles and twigs of the European yew, *T. baccata*, yielding approximately 1 kg of 10-DAB from 3000 kg of needles [57]. He subsequently developed a four-step semisynthetic route from 10-DAB [58]. Building upon this work, the Holton-Ojima team [59] further developed the method, leading to Bristol-Myers Squibb's commercially available paclitaxel production process [60] (Fig. 3). This process involved initially protecting the two hydroxyl groups of 10-DAB, followed by combination with optically active *β*-lactam, ultimately yielding PTX with a 90% yield.

2.3.2. Total synthesis of (−)-PTX

At present, PTX is primarily obtained through plant extraction and semi-synthesis, but its raw materials are scarce and expensive. Consequently, developing an efficient and streamlined total synthesis route is essential for the preparation and bioactivity investigation of PTX and its derivatives. Structurally, PTX features a highly oxygenated [6–8–6–4] core with 11 stereocenters, seven of which are contiguous chiral centers [61, 62]. Furthermore, the strained bicyclo [5.3.1] undecane ring system, with a bridgehead double bond, represents a unique structural feature [63]. These characteristics render PTX a formidable synthetic target.

In recent decades, significant advancements have been made in the total synthesis of PTX. Twelve landmark total synthe-

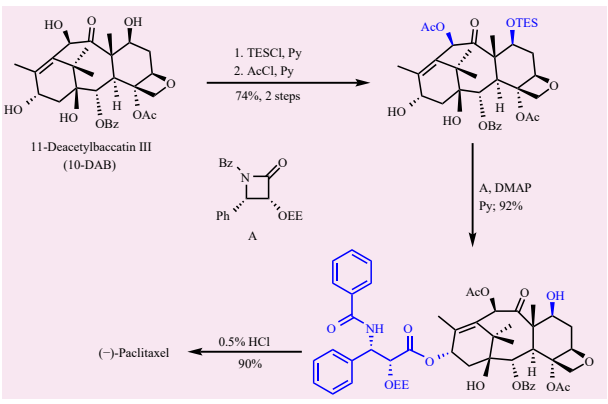

Fig. 3 Holton and Ojima's semi-synthesis of (−)-PTX.

ses [64-83] and three sophisticated formal syntheses [84-87] have been documented. Additionally, more than 60 research groups worldwide have contributed to synthetic studies on PTX, underscoring its importance in the scientific community.

In this review, we present a concise overview of eight-membered ring construction methods employed in total synthesis routes (Fig. 4). In 1994, the Nicolaou research group achieved the first total synthesis of PTX, utilizing a convergent strategy with McMurry coupling as the key approach to construct the challenging octahedral ring at the C9–C10 position [64-68]. Simultaneously, the Holton research group employed the Grob fragmentation reaction as their primary strategy for octahedral ring formation [69, 70]. The Danishefsky research group applied the Heck coupling reaction [71, 72], while Wender's team also utilized Grob fragmentation as their central approach [73, 74]. The Mukaiyama research group opted for a samarium (II) iodide-mediated aldol reaction to construct the octahedral ring [75], while Kuwajima's team employed Mukaiyama aldol reactions [78], and Kshi's team utilized NHK coupling reactions [88]. Baran's team implemented a "two-phase" synthesis method combining a convergent strategy with a type II Diels-Alder reaction [79]. Li's research group used samarium (II) iodide-mediated phenolic coupling to form the C1–C2 bond [80], and Chida's team revisited their total synthesis strategy using samarium (II) iodide-mediated reduction-cycloaddition reactions [81]. Inoue's team adopted a Ti (III)-mediated furyl coupling reaction [82]. In the same year, another successful total synthesis of PTX was accomplished using Pd-catalyzed cyclization [83].

The total synthesis of PTX presents a formidable challenge for organic synthetic chemists, who have undertaken extensive and meticulous investigations spanning over a decade. As technology continues to progress, it is expected that future innovations would lead to more refined and efficient approaches for the total synthesis of PTX.

3. Physiochemical properties and *in vivo* fate of PTX and its derivatives

3.1. Physicochemical properties of PTX and its derivatives

Despite its potent anti-cancer activity, the clinical development of PTX is constrained by its physicochemical properties,

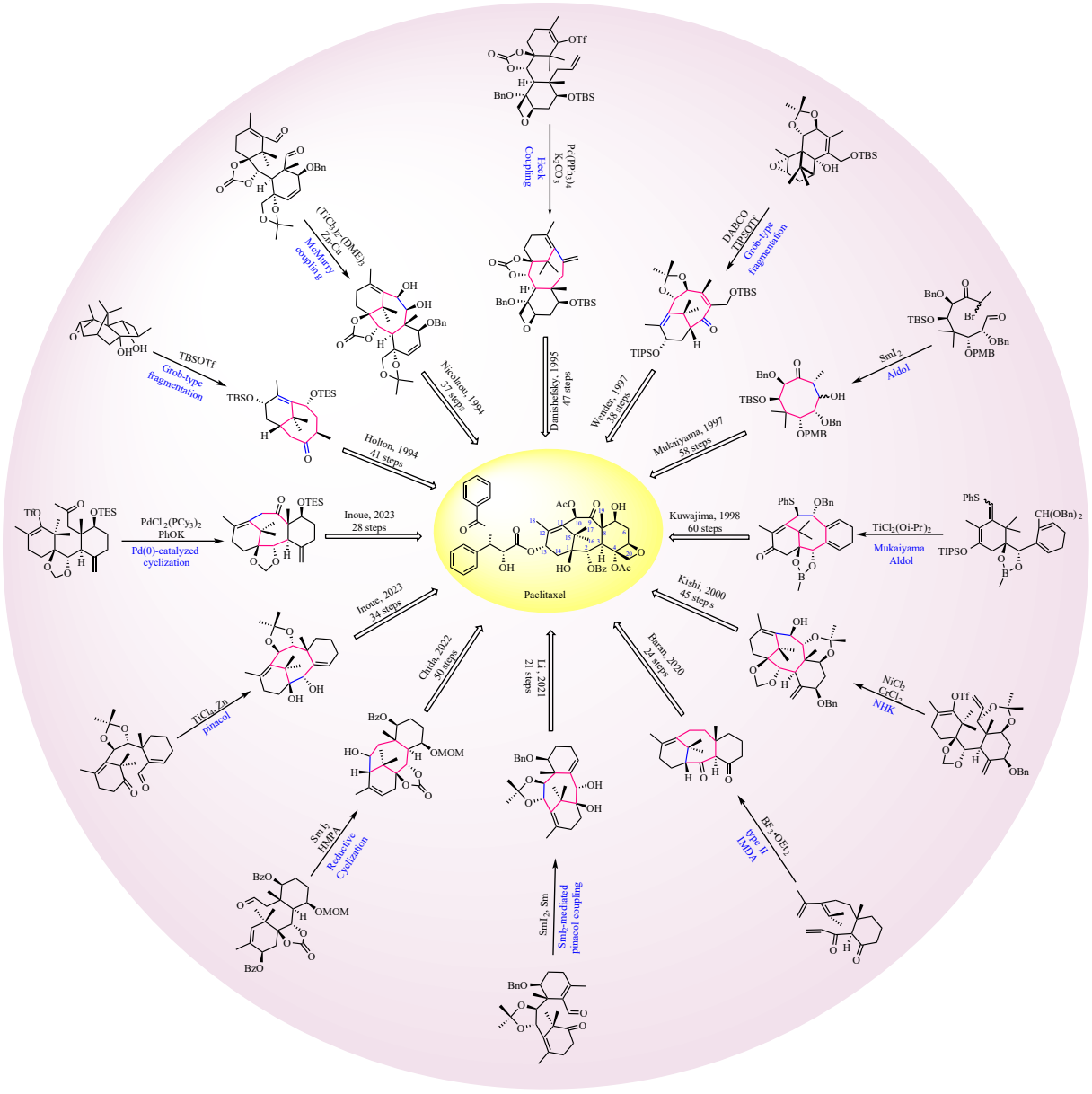

Fig. 4 The total synthesis of PTX.

which are incompatible with the aqueous environment of the human body [89]. A significant challenge is its low solubility in aqueous solutions, which complicates intravenous infusion requiring a medium with specific polar characteristics [90]. As a small hydrophobic molecule, PTX exhibits extremely low water solubility (5.56×10^{-3} g·L^{-1}) [89], resulting in poor distribution and pharmacokinetic challenges in clinical applications [8, 91, 92].

These physicochemical properties also contribute to adverse effects, including neuropathy and kidney toxicity, which substantially restrict the widespread clinical application of PTX and its derivatives [93]. To overcome these limitations, more effective strategies are urgently required for PTX's clinical chemotherapy applications. Two primary advancements have been developed: (i) the design and synthesis of PTX-releasing compounds, known as prodrugs, which exhibit enhanced physicochemical properties [94]. These prodrugs are engineered to improve solubility in aqueous solutions and release PTX within the tumor microenvironment. (ii) Various delivery systems are utilized to encapsulate and transport PTX in the aqueous milieu of the human body, thereby enhancing solubility and delivery efficiency.

3.2. In vivo fate of PTX and its derivatives

Initial administration of PTX, formulated in a vehicle comprising 50% polyoxyethylated castor oil and 50% ethanol, was typically conducted *via* intravenous or intraperitoneal instillation. Following infusion, plasma concentrations of PTX rapidly decline, commencing immediately upon cessation [95, 96]. PTX exhibits widespread distribution to various organs, including the heart, liver, spleen, lungs, kidneys, intestines, and muscles; however, it does not significantly accumulate in the brain or testes. Notably, PTX and its metabolites demonstrate the ability to traverse the human placenta, resulting in fetal exposure [97, 98].

PTX undergoes metabolism by P450s in the human liver, with its metabolites subsequently excreted in bile [99]. The enzyme CYP2C8 catalyzes the formation of the primary metabolite, 6*α*-hydroxy-PTX (6*α*-OHP), while CYP3A4/5 catalyzes the formation of 3'-*p*-hydroxy-PTX (3'-*p*-OH-PTX), a structural isomer [100, 101]. These metabolites are further transformed into a minor metabolite, 6*α*,3'-*p*-dihydroxy-PTX (6*α*,3'-*p*-di-OH-PTX) [101]. MacEachern-Keith et al., in their study on PTX stability, identified 7-*epi*-PTX as the primary metabolite under physiological conditions, resulting from epimerization at C7 [102]. Research by Zhang et al. revealed that CYP2C8 and CYP3A4 participate in the biotransformation of 7-*epi*-PTX in human liver microsomes [103]. Metabolite formation varies across different models due to differences in metabolic gene expression. In human liver microsomes, 6*α*-OHP was the predominant and unique metabolite, whereas C3'-OHP was observed in rats, and a distinct hydroxypaclitaxel metabolite was found in pigs and minipigs *in vitro* [104]. Meng et al. identified four hydroxylated metabolites in rats: 3'-*p*-OHP, 2-OHP, 6*α*-2-di-OHP, and 6*α*-5"-di-OHP, with 6*α*-OHP not detected [105].

PTX represents a significant milestone in anti-cancer drug development; however, its oral administration presents challenges due to poor solubility and intestinal permeability, creating substantial obstacles in current oral drug delivery systems. To enhance oral bioavailability, researchers have explored various strategies [106], as outlined below. While oral administration offers superior patient comfort, PTX's oral bioavailability remains below 10%, limiting its therapeutic efficacy [107]. Consequently, there is an urgent need to optimize and develop novel oral PTX formulations to improve solubility and bioavailability. Different PTX formulations contribute to variations in pharmacokinetics and tissue distribution. Li et al. examined the potential effects of four PTX formulations: nab-PTX (albumin-bound nanoparticles PTX), pac-T (a cremophor EL solvent-based formulation), pac-P (a micellar formulation of PTX encapsulated in the proprietary retinoid compound XR-17), and pac-G (polymeric micellar PTX) [108]. Each nanoformulation yielded distinct plasma exposures and tissue distributions. The efficiency of PTX delivery also varied depending on the formulation employed.

4. Anti-cancer mechanisms

PTX is a widely recognized mitotic inhibitor [109], which arrests cells in the G_2 and M phases of the cell cycle. This process activates pro-apoptotic signaling, ultimately leading to cell death [110, 111]. Beyond inducing cell cycle arrest and apoptosis, PTX has demonstrated the ability to trigger autophagic cell death, pyroptosis, and other forms of cellular demise [112]. This review examines the recently elucidated mechanisms of cell death (Fig. 5).

Apoptosis is the primary form of cell death induced by chemotherapeutic agents [113]. Reactive oxygen species (ROS), crucial metabolic intermediates, play a vital role in regulating cell proliferation and death. Increased ROS production from the endoplasmic reticulum is a key characteristic of ER stress [114]. Excessive ROS leads to oxidative DNA damage, triggering apoptosis. Pro-apoptotic proteins such as BAX, BAK, and BOK oligomerize in the mitochondrial outer membrane, resulting in its permeabilization and the release of cytochrome C [115]. Cytochrome C subsequently binds to apoptotic protease activating factor 1 (APAF1) and pro-caspase-9, activating caspases like caspase-3 and caspase-7, ultimately inducing apoptosis. PTX can directly induce mitochondrial permeability transition and ROS generation [116]. Zhang et al. demonstrated that PTX enhances ROS accumulation, regulates HIF-1α expression, and activates the c-Jun *N*-terminal kinase (JNK)/caspase-3 pathway, leading to apoptosis in prostate cancer cells [117]. PTX also activates the JNK-dependent pathway to induce apoptosis in various cell types, including human head and neck squamous cell carcinoma (HNSCC) OEC-M1 cells, human monocytic leukemia U937 cells, patient-derived chronic lymphocytic leukemia cells, and human thyroid carcinoma 8305C cells [118-120]. In gastric cancer AGS cells, PTX activates caspase-3, caspase-9, and PARP, subsequently inducing apoptosis [121]. While caspase activation is a crucial event in apoptotic cell death [122], PTX can also induce apoptosis through a caspase-independent mechanism in human non-small cell lung cancer (NSCLC) NCI-H460, ovarian carcinoma SKOV3, and breast carcinoma MCF7 cells [123, 124].

ROS can inhibit the phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway, thereby mediating apoptosis in cancer cells [125, 126]. In human breast cancer MCF-7 and canine mammary gland tumor CHMm cells, PTX inhibited the PI3K/AKT signaling pathway, reducing cell viability and proliferation and inducing apoptosis [127, 128]. mTOR, a central regulator of cell growth and proliferation, typically exhibits activated signaling in cancers [129]. Inhibition of mTOR can trigger apoptosis [130]. The PI3K/AKT/mTOR pathway is a canonical signaling pathway, and PTX can promote apoptosis in FLT3-ITD$^+$ acute myeloid leukemia (AML) MV-4-11 cells by inhibiting this pathway [131].

The p53 protein is a well-established regulator of cell death. Wu et al. demonstrated that p53 enhances PTX sensitivity in papillary thyroid carcinoma both *in vitro* and *in vivo* through p53-dependent apoptosis [132]. Long non-coding ribonucleic acid maternally expressed gene 3 (lncRNA MEG3) has been identified as a potential therapeutic target for osteosarcoma [133]. Xu et al. revealed that PTX upregulates MEG3, which subsequently activates p53, leading to apoptosis in human lung cancer A549 cells [134]. Tumor protein p53 inducible nuclear protein 1 (TP53INP1) functions as a tumor suppressor and pro-apoptotic protein [135]. In human giant cell tumors of bone Hs 737.T cells, PTX significantly elevates TP53INP1 expression, promotes p53 phosphorylation, and induces apoptosis in a caspase-dependent manner [136].

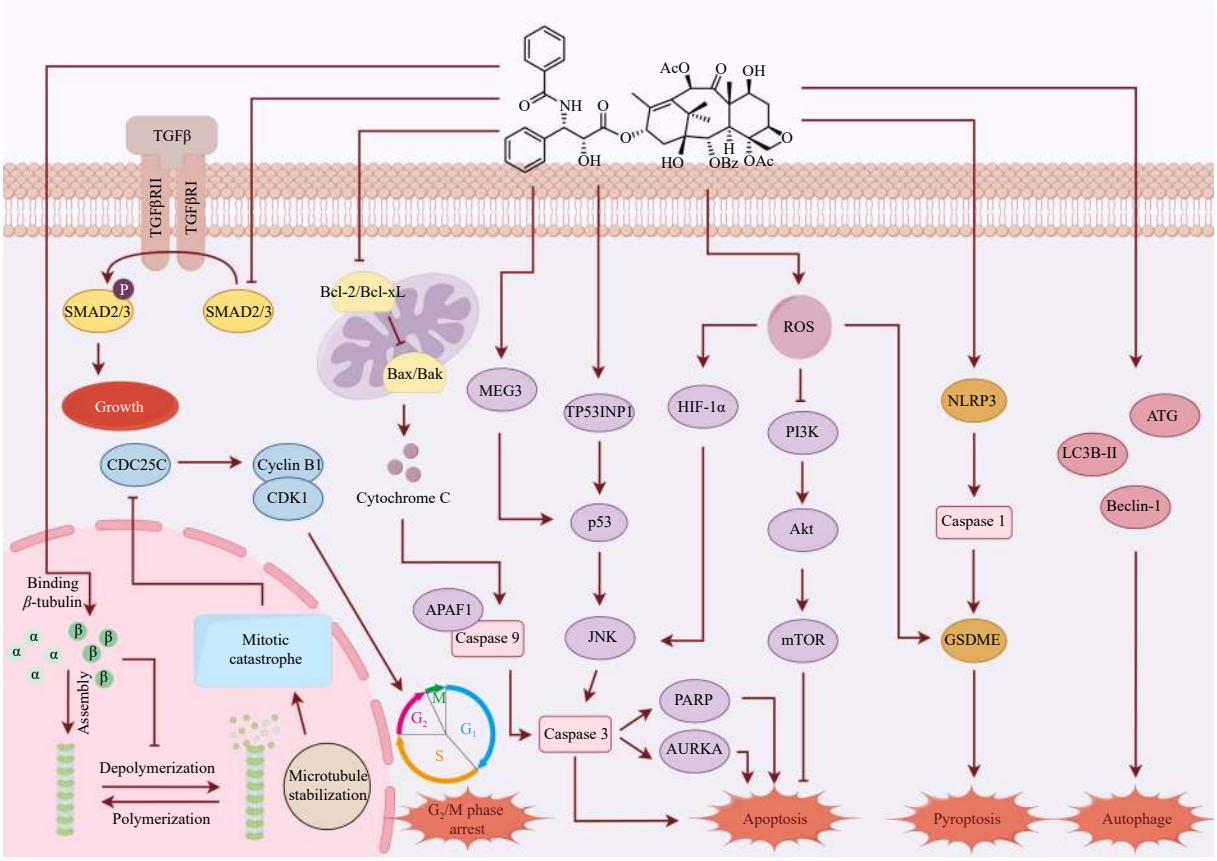

Fig. 5 Anti-cancer mechanism of PTX.

Aurora kinase A (AURKA), a potent oncogene within the serine and threonine kinase family, regulates tumor cell death and represents a promising therapeutic target [137, 138]. Caspases 3/7/8 induce Asp^{132}-cleavage of AURKA, leading to disruption of centrosome formation and spindle assembly, thereby triggering apoptosis [139]. In comparison to the $AURKA^{WT}$ group, the $AURKA^{D132A}$ group exhibited no significant alteration in cancer cell proliferation and apoptosis following PTX treatment, indicating that PTX induces cell apoptosis dependent on Asp^{132}-cleavage of AURKA.

In addition to apoptosis, pyroptosis represents another form of programmed cell death mediated by a family of pore-forming proteins known as gasdermin (GSDM) [140]. Both gasdermin D (GSDMD) and gasdermin E (GSDME) play critical roles in pyroptosis [141]. In human lung cancer A549 [142] and human ovarian cancer A2780 cells [143], PTX induces pyroptosis through caspase-3/GSDME activation. In gastric cancer SNU-719 cells, PTX activates the NLRP3/caspase-1/GSDME pathway [144], while in nasopharyngeal carcinoma HNE-2 and 5-8F cells, it activates the caspase-1/GSDMD pathway [145]. Moreover, ROS activation can induce pyroptosis through GSDMD [146]. Pyroptosis represents a novel pathway of programmed cell death and has the potential to enhance the effects of current clinical agents. Indeed, pyroptosis is a significant mechanism through which chemotherapy drugs treat tumors. Olaparib, a PARP1 inhibitor used for cancers with BRCA mutations, such as prostate, breast, and ovarian cancers, can activate caspase-3 and cleave GSDME, thereby inducing pyroptosis in prostate cancer cells [147]. AT7519, identified from the Approved Drug Library and Clinical Compound Library, induces GSDME cleavage mediated by caspase-3, triggering pyroptosis in glioblastoma multiforme cells [148].

Tumor metastasis remains the primary cause of mortality among cancer patients [149]. Consequently, there is an urgent need for effective strategies to prevent and treat metastatic cancer. Research has shown that circ-IGF1R, comprising Exon 2, significantly impedes the invasion and migration of lung cancer cells [150]. VANGL2, a key component of the planar cell polarity (PCP) complex, has been linked to various types of cancer [151]. In a study by Xu et al., RBFOX3, a neuronal splicing regulator, was found to bind to the precursor messenger RNA (pre-mRNA) of IGF1R, thereby increasing circIGF1R levels [152]. The elevated circ-IGF1R subsequently upregulates VANGL2 by sponging miR-1270, modulates the Wnt pathway, and inhibits the invasion and migration of NSCLC cells [153]. Additionally, their findings indicate that PTX significantly elevates both RBFOX3 protein and circ-IGF1R levels.

5. PTX: clinical application and clinical trials

5.1. PTX therapeutics in the clinic

As a fundamental class of antineoplastic agents, PTX disrupts the microtubular network, promotes cell apoptosis, induces autophagic cell death, and pyroptosis, ultimately exhibiting potent anti-tumor properties [154]. Since its discovery, PTX and docetaxel have been extensively utilized in treating various solid tumors, including breast cancer, NSCLC, pancreatic adenocarcinoma, gastric cancer, prostate cancer, esophageal and esophagogastric junction cancers, biliary tract cancers, cervical cancer, melanoma, and ovarian cancer. However, cabazitaxel is currently indicated solely for prostate cancer. Novel formulations of PTX, such as liposomes, albumin-bound PTX, micelles, nanoparticles, and oral liquids, have significantly contributed to treating various tumors due to their enhanced efficacy and safety profiles. A comprehensive summary of approved PTX, docetaxel, and cabazitaxel formulations employed in clinical practice is presented in Table S1.

5.1.1. Breast Cancer

Breast cancer represents the most prevalent malignancy

among women and constitutes a substantial threat to women's health. PTX and docetaxel serve as fundamental antineoplastic agents in breast cancer treatment, playing crucial roles in neoadjuvant therapy and systemic treatment for human epidermal growth factor receptor 2 (HER2)-positive, hormone receptor (HR)-positive, and triple-negative breast cancer (TNBC).

In the systemic management of advanced HER2-positive breast cancer, chemotherapy is frequently administered in conjunction with HER2-targeted therapy, with PTX being a common component of chemotherapy regimens. Nab-PTX is generally the preferred choice, either as a monotherapy or as part of combination chemotherapy. For patients capable of tolerating dual chemotherapy agents, the combination of docetaxel, capecitabine, and trastuzumab typically demonstrates favorable efficacy.

The multicentre phase III b PERUSE (PERtUzumab global SafEty) study (NCT01572038) evaluated patients with unresectable HER2-positive locally advanced or recurrent breast cancer who had not received prior systemic therapy. These patients were treated with docetaxel, PTX, or nab-PTX in combination with trastuzumab and pertuzumab. The study demonstrated comparable overall response rates (ORRs) for PTX and nab-PTX (docetaxel 79%, PTX 83%, nab-PTX 77%) and similar progression-free survival (PFS) (docetaxel 19.6 months, PTX 23.0 months, and nab-PTX 18.1 months), with comparable safety profiles [155]. Nab-PTX is particularly recommended for patients with allergies to polyethylated castor oil solvent, as it seldom induces allergic reactions and eliminates the need for routine premedication.

In advanced TNBC, PTX is frequently combined with other classic chemotherapy agents such as doxorubicin, carboplatin, gemcitabine, and capecitabine. Nanoparticle albumin-bound PTX (nab-PTX) in combination with carboplatin is the preferred first-line treatment. This regimen has shown efficacy even in patients who have previously experienced treatment failure with PTX injection, PTX liposomes, or docetaxel injection. Currently, there is an increasing trend towards combining chemotherapy with immunotherapy in TNBC treatment. Numerous studies have investigated the efficacy and safety of PTX in combination with programmed cell death protein 1 (PD-1) inhibitors (such as pembrolizumab, tislelizumab, camrelizumab, and toripalimab) and programmed death-ligand 1 (PD-L1) inhibitors (including atezolizumab and durvalumab) [156].

The multicenter phase II cTRIO clinical trial (ChiCTR-2100041675) investigated the efficacy and safety of the PD-1 inhibitor tislelizumab in combination with nab-PTX and carboplatin for neoadjuvant or adjuvant therapy in Chinese TNBC patients. Concurrently, the randomized, double-blind, multicenter phase III TORCHLIGHT trial compared toripalimab plus nab-PTX against placebo in advanced TNBC treatment. Promising results from these trials, presented at the 2023 ASCO annual meeting, indicate that China-developed PD-1 inhibitors may have an expanded role in combination therapies for advanced TNBC. Notably, nab-PTX may be preferable when combined with immune checkpoint inhibitors, as the corticosteroid premedication required for PTX injection, liposomal PTX, and docetaxel injection could potentially impact immunotherapy efficacy.

PTX-containing chemotherapy regimens may be preferred as initial treatment for patients with advanced HR-positive breast cancer who have developed metastases or do not respond to endocrine therapy. In summary, nab-PTX has shown superior efficacy and safety compared to PTX injection or PTX liposomal in both systemic and neoadjuvant treatments for breast cancer. In elderly patients with lower chemotherapy tolerance, the weekly regimen of nab-PTX is generally well-tolerated. Recently, the prospective NABUCCO study demonstrated that nab-PTX treatment in HR-positive/HER2-negative breast cancer resulted in good effectiveness with a low incidence of peripheral neuropathy (only 4.7% of grade 3/4 peripheral neuropathy) [157]. Due to limited evidence supporting nab-PTX use in adjuvant breast cancer therapy, PTX injection remains more commonly recommended. Rugo et al. conducted a clinical trial comparing PTX oral solution plus encequidar with conventional PTX injection for treating patients with metastatic breast cancer. The study found that the oral solution plus encequidar improved PFS and OS with reduced frequency and severity of neuropathy [158].

5.1.2. Gastric cancer

China is experiencing a gradual increase in the incidence of gastric cancer. Both PTX injection and docetaxel injection are available taxanes for treating gastric cancer. For resectable gastric cancer patients, the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel) is preferred for preoperative chemotherapy in Western countries. Recently, the phase III PRODIGY study demonstrated that neoadjuvant chemotherapy with the DOS regimen (docetaxel, oxaliplatin, and S-1), followed by surgery and adjuvant S-1 chemotherapy, significantly improved PFS and OS in resectable locally advanced gastric cancer in Asia. The 8-year PFS rate was 55.8% *vs* 43.2% (P = 0.016), and the 8-year OS rate was 63.8% *vs* 54.6% (P = 0.027) [159]. Consequently, the docetaxel-containing DOS regimen may be recommended as the standard neoadjuvant chemotherapy option in Asia. Additionally, PTX plus carboplatin is recommended for preoperative chemoradiation. However, for unresectable locally advanced, recurrent, or metastatic gastric cancer, neither PTX nor docetaxel is preferred as first-line treatment. Both drugs play significant roles in second-line salvage therapy for patients with advanced gastric cancer who have not responded to first-line chemotherapy.

Recent advancements have been made in chemotherapy regimens incorporating docetaxel or PTX, combined with HER2-targeted therapies and immunotherapy, for specific gastric cancer types. The KEYNOTE-061 [160] and KEYNOTE-063 [161] trials, both randomized, open-label, phase 3 studies, investigated the efficacy and safety of pembrolizumab *vs* PTX as second-line therapy for advanced gastric or gastroesophageal junction cancer. Results indicated that pembrolizumab did not significantly improve median OS, median PFS, or objective response rate in patients with a combined positive score (CPS) of PD-L1 ≥ 1. No evidence suggested that PD-1 inhibitor monotherapy is comparable to single-agent chemotherapy. Given that pembrolizumab did not significantly outperform PTX in efficacy and is substantially more expensive, PTX remains a crucial option in the second-line treatment of advanced gastric cancer.

While PD-1/PD-L1 inhibitor monotherapy as second-line therapy did not significantly extend OS or PFS in PD-L1-positive gastric cancer patients, combination therapy with pembrolizumab and PTX demonstrated enhanced efficacy. Gou et al. conducted a single-arm, phase II study investigating the efficacy and safety of a PD-1 inhibitor combined with nab-PTX and apatinib for second-line treatment in patients with metastatic gastric cancer [162]. The study incorporated various PD-1 inhibitors: pembrolizumab (n = 9), nivolumab (n = 9), sintilimab (n = 20), and camrelizumab (n = 5). The findings revealed significantly prolonged PFS and OS compared to previous studies, indicating that the three-drug combination may be more advantageous than PTX monotherapy or a two-drug regimen.

PTX was initially administered solely through intravenous infusion until the oral formulation (Liporaxel®, DHP107) received approval in South Korea in 2016 for locally advanced, metastatic, and recurrent gastric cancer. This represented the first oral formulation of PTX worldwide, utilizing self-emulsifying drug delivery systems. The DREAM study, a multicenter, prospective, phase III clinical trial, evaluated the efficacy and safety of the PTX oral formulation [163]. Patients with unresectable or recurrent advanced gastric cancer were randomly assigned to receive either DHP107 (200 mg·m^{-2} orally twice daily on days 1, 8, and 15 every

4 weeks) or PTX solution (175 mg·m^{-2} intravenously on day 1 every 3 weeks). The results confirmed that the oral formulation of PTX demonstrated comparable efficacy, safety, and pharmacokinetics to the intravenous solution. This led to its rapid approval for second-line therapy in advanced gastric cancer. In September 2024, PTX oral solution received marketing approval in China based on a randomized, open, parallel-controlled, non-inferiority, multicenter phase III clinical trial (CTR20190050) conducted across 53 hospitals in China. This trial demonstrated that the oral solution not only exhibited efficacy comparable to the intravenous formulation but was also well-tolerated. The availability of the PTX oral solution may enable some gastric cancer patients to undergo home chemotherapy.

5.1.3. Pancreatic adenocarcinoma

Pancreatic cancer is a highly lethal malignancy, with systemic therapy serving as the primary treatment approach. The phase III MPACT trial resulted in the approval of nab-PTX plus gemcitabine as a first-line treatment option for patients with metastatic pancreatic cancer. Long-term follow-up of the MPACT trial demonstrated superior OS with the combination of nab-PTX and gemcitabine compared to gemcitabine monotherapy [164]. At present, gemcitabine plus nab-PTX is recommended for adjuvant therapy of resectable pancreatic cancer, as well as for first-line and second-line therapy of locally advanced and metastatic pancreatic cancer [165].

Recent years have witnessed the development of strategies to convert borderline resectable or locally advanced pancreatic cancer into resectable disease. Research is ongoing to determine the suitability of gemcitabine plus nab-PTX for neoadjuvant treatment of pancreatic cancer. The multicenter, randomized phase II trial NEOLAP-AIO-PAK-0113 (NCT02125136) [166] compared nab-PTX plus gemcitabine with nab-PTX plus gemcitabine followed by FOLFIRINOX (5-fluorouracil + leucovorin + irinotecan + oxaliplatin) for induction chemotherapy in advanced pancreatic cancer patients. The findings suggested that nab-PTX plus gemcitabine was comparable in efficacy and safety to the combination of nab-PTX plus gemcitabine followed by FOLFIRINOX, inducing resection in approximately one-third of patients. A multicenter retrospective study by Weniger et al. demonstrated that patients with locally advanced pancreatic cancer treated with a neoadjuvant regimen of nab-PTX plus gemcitabine exhibited significantly higher resection rates than those treated with gemcitabine monotherapy (81.6% *vs* 43.8%, P = 0.005) [167]. A phase I/II open-label trial identified AM80, a synthetic retinoid, as a promising enhancer of chemosensitivity and drug distribution for the gemcitabine plus nab-PTX regimen [168]. Multiple clinical trials have confirmed the efficacy and safety of nab-PTX for all stages of pancreatic cancer [169]. While docetaxel is recommended only for advanced unresectable pancreatic cancer, other formulations of PTX are seldom employed in pancreatic cancer treatment.

5.1.4. NSCLC

PTX injection, PTX liposome, nab-PTX, and docetaxel are utilized as first-line chemotherapy for NSCLC. The combination of PTX and cisplatin remains a classic treatment option for advanced NSCLC. PTX liposome and nab-PTX demonstrate reduced toxic side effects and fewer allergic reactions compared to PTX injection [170, 171]. In the phase III KEYNOTE-407 study (NCT02775435) [172], NSCLC patients were randomly assigned to receive either pembrolizumab or placebo, combined with PTX/nab-PTX and carboplatin every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to 35 cycles. The results indicated that pembrolizumab plus chemotherapy improved OS and PFS, with extended PFS (6.3 months *vs* 5.9 months), increased ORRs (62.2% *vs* 38.8%), and a higher 5-year OS rate (18.4% *vs* 9.7%). Nab-PTX may be substituted for PTX or docetaxel in patients who have experienced hypersensitivity reactions after receiving these drugs despite premedication, or when standard premedication is contraindicated. In recent years, targeted therapy or immunotherapy combined with chemotherapy has emerged as a significant option for first-line treatment of NSCLC. Clinical trials have investigated the efficacy and safety of PD-1/PD-L1 inhibitors, including camrelizumab, pembrolizumab, serplulimab, nivolumab, tislelizumab, and atezolizumab, combined with PTX-containing chemotherapy, demonstrating substantial survival benefits and improved safety for patients with advanced squamous cell carcinoma and adenocarcinoma [173, 174].

Beyond its application in NSCLC, PTX serves as a subsequent treatment option for SCLC under specific conditions [175]. In 2023, Annic et al. conducted a retrospective multicenter real-life study, EpiTax, which demonstrated the efficacy of the epirubicin-PTX combination regimen for extensive-stage small-cell lung cancer. The study reported a PFS of 11 weeks, an OS of 23 weeks, and an ORR of 34.5%. These results indicate that PTX offers promising therapeutic alternatives for second- and subsequent-line treatments in small cell lung cancer [176].

5.1.5. Prostate cancer

Prostate cancer represents the most prevalent urological malignancy among men, exhibiting a high incidence rate, particularly in middle-aged and elderly populations. The primary treatment for castration-resistant prostate cancer involves a combination of endocrine therapy and chemotherapy, with docetaxel serving as the first-line chemotherapeutic agent for metastatic advanced prostate cancer. Recent advancements in research have led to an expanded application of docetaxel across various stages of prostate cancer, resulting in substantial improvements in patient prognosis.

While chemotherapy is generally not recommended for asymptomatic patients, the SPCG-14 trial investigated the treatment of hormone-naïve, non-metastatic prostate cancer patients with elevated prostate-specific antigen (PSA) using 5 years of bicalutamide, with or without docetaxel. The incorporation of docetaxel led to reduced PSA levels and improved PFS, indicating that docetaxel may be considered for patients exhibiting signs of rapid disease progression, even when symptoms are absent [177].

However, certain studies challenge the efficacy of docetaxel in high-risk non-metastatic prostate cancer. The phase III RTOG 0521 trial, involving 563 eligible patients, compared two treatment regimens: androgen deprivation therapy (ADT) + external beam radiation therapy (EBRT) + docetaxel and ADT + EBRT alone. After a median follow-up of 10.4 years, no significant differences emerged in 10-year survival, disease-free survival, incidence of distant metastasis, or PSA recurrence between the groups. Consequently, the researchers suggested that the application of docetaxel for localized high-risk prostate cancer warrants further investigation [178]. In a separate study, Peltekian et al. [179] examined 137 prostate cancer patients treated with docetaxel, revealing incidence rates of 25% for FN and 33% for neutropenia, substantially higher than previously reported. This research underscored the necessity for regular blood count monitoring to detect neutropenia and advocated for preventive measures when administering taxane-based chemotherapy.

Cabazitaxel, a novel taxane, has been approved exclusively for metastatic castration-resistant prostate cancer (mCRPC) in patients previously treated with docetaxel-containing regimens. The phase III FIRSTANA trial (NCT01308567) evaluated the OS of cabazitaxel at 20 or 25 mg·m^{-2} compared to docetaxel at 75 mg·m^{-2} in mCRPC patients. The findings revealed that cabazitaxel at 20 mg·m^{-2} did not demonstrate superior OS but exhibited reduced toxicity compared to docetaxel [180]. Unlike other taxanes, cabazitaxel exhibits a low affinity for multi-drug-resistant proteins. For patients experiencing disease progression during or

after docetaxel treatment and with adequate life expectancy, cabazitaxel is recommended. Due to its lower toxicity profile and improved quality of life outcomes, mCRPC patients often prefer cabazitaxel over docetaxel [181]. Moreover, cabazitaxel has shown superiority to hormone therapies such as abiraterone or enzalutamide in mCRPC patients who have failed docetaxel treatment [182]. Current research is exploring cabazitaxel's potential in other stages of prostate cancer, including neoadjuvant therapy [183]. As cabazitaxel has not yet received approval in China, Chinese pharmaceutical companies are actively developing cabazitaxel injections, with several clinical trials underway (NCT03258320).

5.1.6. Other cancers

PTX has been extensively utilized in the treatment of various cancers, including esophageal, biliary tract, cervical, melanoma, and ovarian cancers. A multicenter, placebo-controlled, randomized phase III trial (NCT03038100) demonstrated that the combination of atezolizumab with PTX, carboplatin, and bevacizumab did not exhibit superior efficacy in treating ovarian, fallopian tube, or primary peritoneal cancers [184]. This finding reinforces PTX's position as a fundamental chemotherapy agent in ovarian cancer treatment. Currently, several clinical trials are recruiting participants to investigate the efficacy and safety of PTX or nab-PTX in biliary tract cancers (NCT06037980, NCT05812430, NCT05757336, NCT05285358). Furthermore, a single-center, single-arm, open-label, phase II clinical trial has been recently registered (NCT06199895) to evaluate the efficacy and safety of PTX PMs for injection in treating advanced carcinomas, including gastric cancer, esophageal carcinoma, and pancreatic adenocarcinoma, that are resistant to taxanes.

5.1.7. Medication safety

As the clinical application of PTX has expanded, adverse drug reactions (ADRs) such as hypersensitivity, bone marrow suppression, gastrointestinal issues, and peripheral neuropathy have become significant concerns. Hypersensitivity is the most prevalent and high-risk ADR associated with PTX injection. The solvent contains two irritating components: 50.3% polyethylated castor oil and 49.7% ethanol, which can readily induce hypersensitivity, including potentially fatal anaphylaxis. Consequently, a triple-drug combination of dexamethasone, H_2 receptor antagonists (e.g., cimetidine), and H_1 receptor antagonists (e.g., diphenhydramine) is routinely administered as premedication before PTX administration. A retrospective analysis by Sa-Nguansai et al. [185] of 3708 patients revealed that the incidence of PTX hypersensitivity reactions was 10.11%, and they developed a clinical scoring model to predict hypersensitivity in cancer patients. High-risk patients identified by this model should undergo close monitoring and receive early prophylaxis. Premedication with corticosteroids or antihistamines is also necessary for PTX liposome, docetaxel, and cabazitaxel injections. However, nab-PTX, which utilizes human serum albumin as the solvent, significantly enhances the solubility and stability of PTX, markedly reducing allergic reactions caused by solvent excipients and improving patient compliance. Consequently, dexamethasone pre-treatment is not required. For patients with prior allergies to PTX or docetaxel, nab-PTX can be administered under close supervision as a viable treatment option [186]. Furthermore, PTX PMs and oral PTX solutions can also substantially reduce the incidence of hypersensitivity [187].

Bone marrow suppression, which includes neutropenia, reduced white blood cell counts, thrombocytopenia, and anemia, is the primary cause of PTX dose reduction or discontinuation. Neutropenia frequently results in fever or infection, while anemia may induce weakness, fatigue, or dyspnea, all of which can interfere with a patient's anti-tumor treatment regimen. In comparison to conventional PTX, nab-PTX demonstrates a significantly lower incidence of grade 4 neutropenia [187].

Gastrointestinal toxicities, including nausea, vomiting, and diarrhea, represent significant side effects of taxane drugs. Additionally, peripheral neuropathy, alopecia, and hepatic impairment may occur, potentially impacting the quality of life for patients undergoing chemotherapy with PTX. Li et al. [188] performed a meta-analysis comparing nab-PTX with conventional PTX injection in breast cancer patients across all stages. Their findings revealed that nab-PTX significantly improved the objective response rate compared to PTX injection. This evidence suggests that nab-PTX may be preferable when the primary aim is to reduce tumor burden in breast cancer patients.

Immunotherapy has become a widely adopted treatment modality for various tumors. However, the influence of glucocorticoids, such as dexamethasone, on immunotherapy remains uncertain. Some researchers have proposed reevaluating the effects of glucocorticoids on immunotherapy, suggesting a preference for limiting or avoiding glucocorticoid use in combination with PTX-based chemotherapy [189]. Additionally, glucocorticoids used for premedication may interact with various CYP3A4 enzyme inhibitors or inducers, potentially compromising drug therapy efficacy. In such scenarios, novel formulations of PTX, including nab-PTX, PMs, and oral solutions (which do not require premedication), may offer significant clinical advantages. These new formulations also provide additional benefits in terms of medication safety. For instance, nab-PTX can be administered at standard doses in patients with mild hepatic impairment or renal injury. When administering PTX preparations, it is crucial to closely monitor the infusion site for extravasation and infiltration to prevent irreversible damage. Notably, PTX PMs rarely cause extravasation at the infusion site.

5.2. PTX therapeutics in clinical trial

Over the past decade, two newly developed taxol analogues larotaxel (XRP9881) and ortataxel (BAY59-8862) have entered into phase II or III clinical trials for the treatment of various tumors. Milataxel (MAC321) and tesetaxel (DJ-927) are also novel taxol analogues, but some researches on the two compounds almost come to an end due to the lack of promising results.

5.2.1. Larotaxel

Larotaxel (XRP9881) is a taxol analog with demonstrated broad-spectrum anti-tumor activity, as evidenced by multiple clinical trials. These trials have encompassed various cancer types, including breast cancer, pancreatic adenocarcinoma, NSCLC, and bladder cancer. In 2008, a phase II multicenter study investigated the anti-tumor efficacy and toxicity profile of larotaxel in patients with metastatic breast cancer who had previously undergone docetaxel- or PTX-based therapy [190]. The study administered larotaxel at 90 $mg{\cdot}m^{-2}$ every three weeks, revealing favorable activity, manageable toxicity, and promising therapeutic efficacy. For lung cancer treatment, larotaxel was evaluated in combination with cisplatin, carboplatin, or gemcitabine for stage IIIb or IV NSCLC in phase I and II trials [191, 192]. The findings indicated that 50 $mg{\cdot}m^{-2}$ of larotaxel could extend median PFS and OS with tolerable adverse events. However, a phase III trial assessing larotaxel combined with cisplatin as first-line treatment for advanced or metastatic urothelial or bladder cancer was prematurely terminated, potentially due to inferior PFS outcomes. Consequently, the clinical development of larotaxel has encountered significant obstacles, and it has not yet achieved market approval [193]. In 2021, Li et al. developed larotaxel nanoliposomes functionalized with a guanine-rich quadruplex nucleotide-lipid derivative, which exhibited prolonged circulatory effects, tumor-targeting properties, and potent anti-cancer activity in breast cancer-bearing mice [194].

5.2.2. Ortataxel

Ortataxel (BAY 59-8862) is a promising taxol analog for the treatment of PTX-resistant cancers, currently undergoing various stages of clinical trials for different tumors. Phase II trials have been conducted to evaluate the efficacy of ortataxel in treating patients with refractory non-Hodgkin's lymphoma (NCT00044551), recurrent glioblastoma (NCT01989884), and PTX-resistant NSCLC (NCT00044538), among others. However, the majority of these trials have not produced favorable outcomes or failed to demonstrate significant superiority in recurrent glioblastoma patients [195]. Recent research is exploring the mechanism by which ortataxel counteracts PTX resistance, potentially through modulation of P-glycoprotein (P-gp) transport and P-gp overexpression [196].

5.3. PTX therapeutics using drug delivery systems (nanoparticles, prodrug)

PTX remains a primary choice in cancer treatment as a crucial adjunct to surgery and radiotherapy. However, as discussed in sections 3.1 and 3.2, its clinical application is constrained by certain physicochemical properties, including poor solubility, low biocompatibility, and systemic toxicity. Reported side effects encompass dyspnea, gastrointestinal reactions, renal toxicity, and myelosuppression [197-199]. Beyond organ and tissue damage, PTX has been demonstrated to impair axonal trafficking of RNA granules [200], induce immunogenic cell death (ICD), elevate alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in mice treated with free PTX [201]. Consequently, developing an effective drug delivery system for PTX is essential to enhance its efficacy and mitigate side effects. In comparison to conventional PTX-based drugs, formulations combining PTX with delivery systems can address hydrophobicity, extend retention time, improve drug loading capacity, and achieve targeted delivery to some extent [202]. These systems may reduce toxicity and side effects by directing the drug specifically to the tumor site.

In recent decades, nanomaterials have been investigated as innovative drug delivery systems for PTX. Numerous nanoparticles employed for this purpose possess dimensions smaller than 200 nm, enabling them to surmount the mucus barrier, thereby enhancing targeting capability and reducing immunogenicity. Furthermore, these nanoparticles demonstrate high loading capacities for hydrophobic anti-cancer drugs and offer protection against biodegradation, rendering them promising candidates for biomedical applications.

Multiple drug delivery systems have been documented for PTX therapeutics [203], encompassing micelles, liposomes, biological nanoparticles, and metallic nanoparticles (Fig. 6). While clinical trials are yet to be conducted, the combination of PTX with functionalized delivery systems is anticipated to emerge as a potent approach in cancer treatment in the future [204].

5.3.1. Micelles

Micelles, also known as PMs, are supramolecular nanoparticles characterized by core-shell structures and a nanoscopic diameter range of 10–200 nm [205, 206]. These structures form through the self-assembly of amphiphilic copolymers with a diblock configuration, comprising a hydrophobic polymer core and a hydrophilic polymer shell. PTX, being a hydrophobic small molecule, can be encapsulated within the hydrophobic polymer core of PMs, thereby enhancing both loading capacity and treatment efficacy.

Micelle-based nanocarriers have demonstrated efficacy in treating various malignancies, including breast cancer [207-209], cervical cancer [210], lung adenocarcinoma [211], colon carcinoma [212], and liver cancer [213]. Polymer micelles composed of amphiphilic copolymers, such as poly (ethylene glycol)-b-poly (ε-caprolactone) (PEG-PCL) [209], 9-fluorenylmethoxycarbonyl-polyethylene glycocholic acid (Fmoc-PEG-GCA) [212], PLA-ss-PEI-FA-ss-PEG [211], and PEG-b-PMPMC-g-PTX (PMP), have been extensively investigated as PTX drug nanocarriers for cancer chemotherapy.

Encapsulation of PTX in micelles has been demonstrated to enhance drug solubility by more than three orders of magnitude [214] and to confer additional advantageous properties for cancer treatment. Burgess et al. established a platform for the continuous production of PMs encapsulating PTX [215], ensuring an average particle size range of 15–70 nm with low polydispersity. This research has the potential to improve the production of high-quality PMs.

The adaptable characteristics of nano drug delivery systems enable the integration of functional groups and molecules into PMs. PTX prodrugs with reduction-sensitive [216], ROS-sensitive [208], and pH-sensitive [217] properties have been successfully incorporated into PMs for cancer treatment. Studies have demonstrated that PTX-coated micelles enhance the *in vivo* retention time of PTX following oral administration [212].

The combination of PTX with other cancer therapies has been proposed as a multifaceted approach to enhance cancer treatment efficacy. These complementary therapies include doxorubicin [211], cancer thermal therapy [218], anti-cancer stem cell (CSC) agents like thioridazine (THZ), and PD-1/PD-L1 inhibitors like HY19991 [219]. This combinatorial strategy may offer a more effective approach to clinical cancer treatment than traditional chemotherapy or immune checkpoint blockade therapy alone.

5.3.2. Liposomes

Liposomes are synthetically produced, spherical vesicular structures composed of lipids. Their membrane comprises single or multiple concentric phospholipid bilayers [220]. Owing to their high biocompatibility and amphiphilic nature, hydrophobic molecules such as PTX can be incorporated into the bilayer membrane, while hydrophilic molecules, like sulforhodamine B, can be encapsulated within the liposome's aqueous core [221].

Liposomes typically range in diameter from 50 nm to 1 μm, with the specific size dependent on the preparation method [222, 223]. In comparison to free drug molecules, liposomes enhance the solubilization of hydrophobic drugs such as PTX, rendering them a versatile drug delivery system. The first commercialized liposomal formulation of PTX was liposomal PTX.

Despite extensive research, the pharmacokinetics of PTX

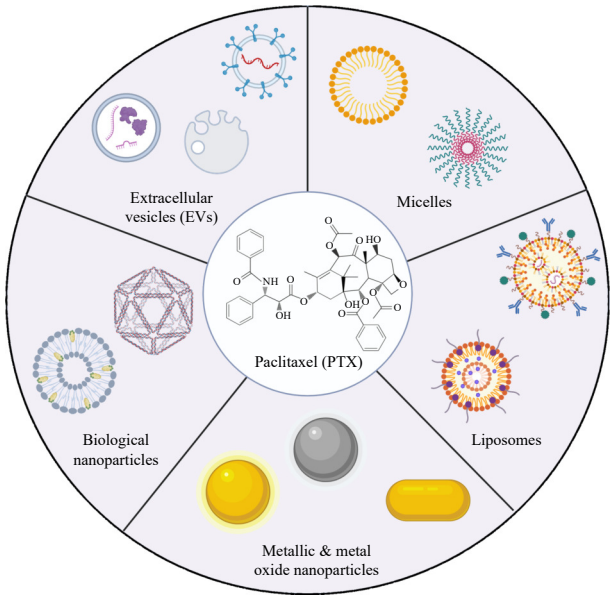

Fig. 6 Drug nanocarrier systems reported for delivery of PTX in cancer therapy.

liposomes remain insufficiently understood, hindering their clinical application. Li et al. [224] investigated the exposure–safety relationship of PTX liposomes in patients with NSCLC. Their findings revealed that the total PTX concentration in plasma initially decreased rapidly, followed by a slower decline, with ultimate metabolism occurring in the liver.

The initial PTX liposome injection, lipusu, has been utilized in clinical treatments for breast cancer, non-small-cell lung cancer, and other malignancies [225]. Subsequently, additional PTX delivery systems based on liposomes have been reported. Shen and Lo et al. [226] engineered a glucosamine-labeled liposomal ceramide to co-deliver PTX and carboplatin, leveraging the upregulation of glucose transporter 1 (GLUT1) on cancer cells. This approach yielded an exceptional synergistic effect, with tumor clearance observed in 75% of the mice. A liposome-based PTX anti-cancer drug, LEP-ETU™, underwent Phase I clinical trials for TNBC treatment [227]. Liposome-based PTX can also be employed in combination therapy with other small molecule drugs. Oliveira et al. [228] examined the optimal co-encapsulation ratio between PTX and doxorubicin, finding that at a 1∶10 ratio, the LD_{50} dose range of the co-encapsulated drug significantly exceeded that of free PTX or doxorubicin.

The delivery of PTX *via* organic nanoparticles, including micelles and liposomes, continues to face challenges related to stability and biological barriers. PTX drugs require stable encapsulation within liposomes to prevent premature release before reaching the target site. Once at the target, efficient drug release is crucial. Moreover, liposome carriers may degrade due to physiological processes [229]. Surface modifications, such as PEGylation, are common strategies to minimize unintended recognition and degradation in the biological environment. Another approach to enhance release efficacy involves the use of response systems, such as pH-dependent and redox-dependent response elements, which accelerate PTX drug release upon reaching the target site.

5.3.3. Biological nanoparticles

Nanoparticles composed of biological materials, including proteins, peptides, and DNAs, have been engineered to deliver PTX for cancer therapy. These biomaterial-based nanoparticles exhibit advantageous properties such as enhanced biocompatibility, improved solubility, biodegradability, reduced side effects, and low immunogenicity [230].

Proteins are prevalent in serum, egg whites, milk, and plant sources, contributing to their high biocompatibility and low toxicity. The abundant active groups on proteins function as reaction sites for binding targeted ligands and tracking dyes [231]. Zhu et al. reported a PTX-loaded bovine serum albumin (BSA) nanoparticle that effectively inhibited the proliferation and migration of osteosarcoma (143B) cells [232]. BSA-based PTX delivery systems have demonstrated efficacy in treating various cancers, including breast [233], cervical [234], glioma [235], esophageal [236], and lung cancer [237]. Li and Xu et al. [238] developed a redox- and metalloproteinases (MMPs) MMP-2-sensitive PTX delivery system based on BSA for inhibiting murine MCF-7 cell lines. This system delivered PTX to the tumor microenvironment and released it in response to specific stimuli. Peptides, like proteins, have also been utilized as drug delivery systems. Zhang and Yu et al. [239] introduced a glutathione (GSH)-responsive peptide nanocarrier capable of co-delivering PTX and pDNA, demonstrating enhanced cell uptake and cytotoxicity. Albumin-bound PTX drugs have emerged as a promising strategy for enhancing anti-cancer efficacy while mitigating cytotoxicity.

In addition to proteins, DNA has also been utilized as a delivery vehicle for PTX. As a genetic material, DNA demonstrates high biocompatibility. The unique property of DNA's base pair complementarities renders it valuable in nanotechnology, particularly in drug nanocarrier systems [240].

DNA nanotechnology, initially introduced by Seeman in 1982 [241], progressed to the synthesis of edge-of-cube-shaped DNA molecules in 1991 [242] and 2D DNA arrays in 1998 [243]. Subsequently, numerous drug delivery systems based on DNA nanotechnology have been developed for cancer treatment. Zhang et al. [244] demonstrated that PTX could be grafted onto a phosphorothiolated DNA backbone through a reaction between the phosphorothioate group and a benzyl bromide group, achieving a high drug loading ratio of approximately 53%. DNA nanostructures with tetrahedral framework nucleic acid (tFNA) have been applied in PTX delivery for treating cancers such as NSCLC and glioblastoma [245-247], demonstrating the broad potential for PTX delivery systems.

Despite the advantages of biological nanomaterials in PTX delivery, several limitations persist for broader clinical applications. A primary constraint is the release strategy for loaded PTX. The high hydrophilicity of these materials results in relatively low drug loading efficacy [248]. Researchers have explored various solutions, including hydrophobic modification and chemical fixation [249]. Another significant challenge, particularly for DNA-based nanoparticles, is the negative surface charge, which impedes cellular uptake and promotes degradation during transport. To address these issues, further optimization strategies require development.

5.3.4. Metallic & metal oxide nanoparticles

Metallic and metal oxide nanoparticles represent promising drug delivery systems due to their small size, high molar extinction coefficients (several orders of magnitude larger than common organic fluorescent dyes), and high surface-to-volume ratio [250]. Various types of metallic nanoparticles, including gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), platinum nanoparticles (PtNPs), and iron oxide nanoparticles, have been extensively investigated for PTX delivery in cancer treatment.

AuNPs have been utilized as anti-cancer drug delivery systems since 2004. Paciotti et al. [251] demonstrated a 32-nm AuNPs carrier system that effectively delivered tumor necrosis factor (TNF) to target and treat colon carcinoma *in vivo*, with minimal accumulation in the liver and other healthy organs in mice. Subsequently, AuNPs have been extensively employed for PTX delivery in various cancers, including glioblastoma [252], breast cancer [253], lung cancer [254], and colon cancer [255]. Moreover, AuNPs exhibit enhanced photothermal therapy (PTT) properties, facilitating the development of combination cancer treatments with chemotherapy. Wang et al. [256] presented an AuNPs and PTX co-delivery system that augmented anti-cancer effects through a chemo-photothermal combination, enhancing biocompatibility, selectivity, intracellular uptake, and cytotoxicity.

In addition to AuNPs, AgNPs have also been utilized as PTX delivery systems in cancer treatment. Park et al. [257] conducted a comparison between folic acid and chitosan-functionalized gold nanorods (AuNRs) and triangular silver nanoplates (AgNPs) for PTX delivery in cervical adenocarcinoma (HeLa) and human colorectal adenocarcinoma (HT-29) cells. Their findings indicated that AgNPs demonstrated higher efficiency than AuNRs in HeLa cells. Qian et al. [258] described an RGD PtNP combined with GSH-responsive PTX for bladder cancer treatment. Their research revealed that PtNPs generated oxygen to enhance photodynamic therapy efficiency, while GSH-responsive PTX release in the tumor microenvironment increased drug accumulation at tumor sites, resulting in improved chemo-photodynamic therapy outcomes for bladder cancer.

Magnetic nanoparticles (MNPs), a category of metallic and metal oxide nanoparticles, have been extensively investigated for

diverse applications, including drug delivery, hyperthermia, and magnetic resonance imaging [259-261]. The unique properties of MNPs are primarily attributed to their intrinsic ferromagnetism [262].

Superparamagnetic iron oxide nanoparticles (SPIONs), a typical example of MNPs, have been widely applied in PTX delivery for cancer treatment, including breast cancer [263-266], melanoma [267, 268], brain tumors [269], cervical cancer [270], and NSCLC [271]. Balan et al. [272] investigated crystalline magnetite conjugates as PTX delivery systems and observed that PTX-loaded SPIONs could sustain drug release over 72 h. It is crucial to recognize that metal nanoparticles can induce genotoxicity in human cells [273], potentially influencing cytotoxicity and anti-bacterial properties due to aggregation and cellular binding. However, protein precoating has demonstrated significant enhancement in stability within biological media, diminishing cytotoxicity and enhancing biocompatibility [274]. Consequently, pre-treatment coating warrants careful consideration for the safer clinical application of metal nanoparticles.

5.3.5. Extracellular vesicles (EVs)

EVs are released by nearly all cells, both prokaryotic and eukaryotic, during normal physiological processes [275]. These vesicles contain various cellular components, including proteins, DNA, and RNA. Exosomes, a typical type of EV, are membrane-bound vesicles with diameters ranging from 50 to 150 nm [276]. They are derived from almost all cell types and play a role in intercellular communication and regulation. Under normal physiological conditions, exosomes participate in immune responses, viral pathogenicity, and the progression of various diseases, including cardiovascular disorders and cancer. This inherent characteristic makes exosomes suitable candidates for therapeutic applications and as drug delivery systems [277, 278].

PTX can be incorporated into exosomes through two primary methods. The first involves the direct release of PTX-containing exosomes through intracellular processing [277, 279]. The second method entails the encapsulation of PTX into cell-derived exosomes [280]. Exosomes originating from various cell types, including NK cells, T cells, M1-macrophages, bovine colostrum, and primary tumors, have been utilized in cancer treatment [276]. The use of exosomes as delivery systems can address challenges such as dose-related toxicity and water insolubility. PTX-exosome formulations demonstrate enhanced anti-cancer activity compared to PTX alone. Gupta et al. [281] reported that, in an orthotopic lung cancer model, PTX administered orally *via* exosomes achieved greater efficacy than conventional intravenous injection.

Exosomes demonstrate versatility in drug delivery, capable of not only transporting PTX independently but also integrating with other delivery systems, including micelles, liposomes, and MNPs [282, 283]. Liu et al. [284] introduced an innovative anti-cancer strategy that combines biomimetic tumor-derived exosomes with liposomes and PTX for the treatment of advanced breast cancer. This approach is further enhanced by thermal therapy utilizing gold nanorods, resulting in improved anti-tumor efficacy in advanced breast cancer cases.

Exosomes have emerged as a promising vehicle for PTX delivery owing to their unique advantages, including diverse functionalities and the potential to facilitate intercellular communication. However, the clinical application of exosomes for drug delivery necessitates further investigation, particularly regarding incorporation stability, responsive drug release mechanisms, and more comprehensive clinical studies [285]. Moreover, the active biomolecules inherently present within or on the surface of exosomes not only enhance PTX delivery but also influence their biodistribution, cellular uptake, and therapeutic mechanisms. The properties of exosomes exhibit significant variability depending on their origin, underscoring the need for additional research to elucidate their intrinsic characteristics.

6. PTX chemo-immunotherapy

6.1. Immune mechanism of action of PTX and its derivatives

PTX, a plant-derived chemotherapeutic agent, is widely utilized in the treatment of various cancers [286]. Renowned for its high efficacy and low toxicity, PTX promotes microtubule polymerization while preventing depolymerization. This mechanism effectively arrests the cell cycle at the G_2/M phase, ultimately inducing apoptosis in tumor cells [287]. Beyond this classical mechanism, PTX has been demonstrated to enhance tumor cell immunogenicity when administered as a pretreatment [288]. The immune mechanism of PTX primarily involves four key steps in the cancer-immunity cycle: enhancing the antigen presentation capacity of antigen-presenting cells, indirectly promoting T-cell activation, reversing immune suppression in the tumor microenvironment, and synergizing with cytotoxic lymphocytes to eliminate tumor cells, as depicted in Fig. 7. Notably, PTX at low doses exhibits significant immunomodulatory effects. It promotes the maturation of dendritic cells (DCs), enhancing their antigen-presenting capabilities and activating T-cell immune responses [289]. The specific mechanisms include the upregulation of co-stimulatory molecules on DCs, such as a cluster of differentiation 80 (CD80) and CD86, and increased secretion of IL-12, which collectively promote T-cell activation and proliferation [290]. Furthermore, PTX can inhibit immunosuppressive cells in the tumor microenvironment, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby enhancing anti-tumor immune responses [291, 292]. By downregulating FoxP3 expression in Tregs and inhibiting MDSC expansion, PTX mitigates the immunosuppressive functions of these cells, further augmenting the anti-tumor activities of T cells and natural killer (NK) cells.

6.2. PTX and its derivatives for potentiated chemo-immunotherapy

The synergy between chemotherapy-induced ICD and immunostimulatory agents has demonstrated significant potential in enhancing T-cell immune responses and anti-tumor activity, particularly in breast cancer [293, 294]. A clinical trial combining nab-PTX and the PD-L1 antagonist atezolizumab showed markedly improved anti-cancer efficacy compared to atezolizumab monotherapy in a Phase III study involving TNBC patients [295]. Nevertheless, chemo-immunotherapy for TNBC faces several challenges, including insufficient selectivity for TNBC, considerable systemic toxicity, and limited ICD induction [296]. To enhance PTX efficacy and mitigate its adverse effects, researchers have developed various PTX derivatives and nano-drug delivery systems. For instance, Qiu et al. developed 5β1 integrin-targeted micellar PTX (ATN-MPTX) to induce potent and selective ICD and chemo-immunotherapy in TNBC. This system utilized the clinically validated ATN peptide as a ligand and reduction-sensitive biodegradable micelles as carriers [209]. ATN-MPTX showed significant targetability and enhanced uptake in α5β1 integrin-positive 4T1 cells, inducing markedly stronger ICD compared to free PTX and non-targeted MPTX. *In vivo* studies using the 4T1 TNBC model demonstrated that ATN-MPTX achieved superior tumor accumulation and treatment efficacy compared to all controls. Notably, combining ATN-MPTX with a nano-STING agonist further augmented the immunotherapeutic effects by increasing proinflammatory cytokine secretion and enhancing $CD4^+$ and $CD8^+$ T cell presence in the tumor and spleen while reducing Tregs. This resulted in significantly improved inhibition of 4T1 primary tumors and a notable reduction in lung metastases.

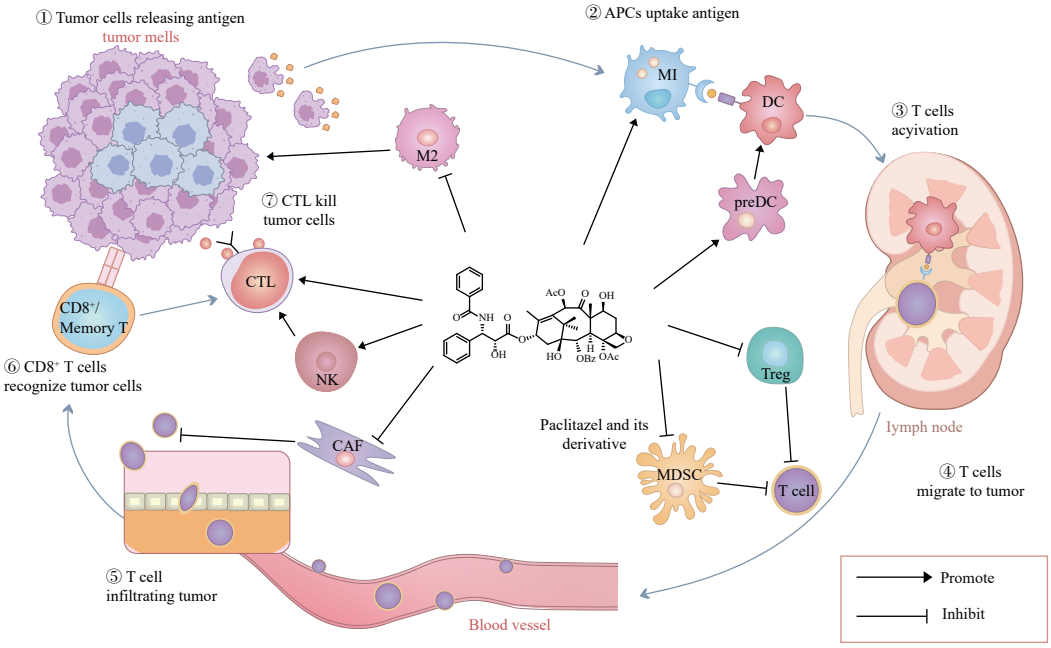

Fig. 7 Immune mechanisms of action of PTX and its derivative.

To address challenges in delivering PTX, such as premature drug release and insufficient tumor accumulation, researchers developed an innovative ROS-activated liposome nanoplatform. This platform incorporated a ROS-sensitive PTX derivative (PSN) loaded into liposomes [297]. The liposomal nanosystem was strategically designed to remotely load BMS-202 (a PD-1/PD-L1 inhibitor) and PSN, enabling ROS-sensitive PTX release and sustained BMS-202 release. *In vivo* studies utilizing an orthotopic 4T1 breast cancer model demonstrated enhanced anti-tumor efficacy.

6.3. Role of PTX and its derivatives in chemo-immunotherapy for clinical applications

Recent studies and experimental data further corroborate the efficacy of PTX as an immunomodulator in clinical applications (Table S2). A Phase III clinical trial demonstrated that nab-PTX combined with immune checkpoint inhibitors significantly extended PFS and OS in patients with metastatic TNBC [295]. The research also indicated that this combination therapy substantially reduced the risk of disease progression and enhanced OS rates for patients [298]. Furthermore, PTX has exhibited promising results in treating other cancer types, including HNSCC and ovarian cancer [299, 300]. In a single-arm Phase II trial (NCT04826679), patients with resectable locally advanced HNSCC (T2–T4, N0–N3b, M0) received neoadjuvant chemo-immunotherapy comprising camrelizumab (200 mg), nab-PTX (260 mg·m^{-2}), and cisplatin (60 mg·m^{-2}) intravenously on day one of each three-week cycle for three cycles [301]. This study achieved its primary endpoint, demonstrating the potential efficacy of neoadjuvant camrelizumab combined with nab-PTX and cisplatin while maintaining an acceptable safety profile in patients with resectable locally advanced HNSCC.

In the treatment of unresectable pancreatic adenocarcinoma, Dai et al. reported a novel chemo-immunotherapy regimen combining nab-PTX + gemcitabine chemotherapy with sequential recombinant interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy [302]. The study demonstrated that the AGIG chemo-immunotherapy regimen yielded favorable ORRs, OS, and manageable toxicities as a first-line therapeutic approach for advanced pancreatic cancer. Jiao et al. assessed the clinical efficacy of combined chemotherapy and immunotherapy in patients with advanced NSCLC, as well as its impact on nutritional status and immune function. The ORRs were 80% and 61% in the study and control groups, respectively, with a statistically significant difference (P = 0.03). The researchers conducted a comparative analysis of clinical effects, adverse reactions, improvement in nutrient indices, and changes in levels of CD3$^+$, CD4$^+$, CD8$^+$, and CD4$^+$/CD8$^+$ ratio in T-lymphocyte subsets between the two groups. Furthermore, PTX has shown synergistic effects when combined with other immunotherapies [303]. For example, research has indicated that PTX combined with CAR-T cell therapy significantly enhances the anti-tumor activity of CAR-T cells [304]. The combination of PTX with other targeted therapies has also exhibited promising therapeutic effects and reduced toxicities [171].

7. Conclusion and prospect

Cancer has emerged as a significant global public health concern, profoundly affecting human health, national economies, and societal development. Population-based cancer survival serves as a crucial indicator for evaluating the efficacy of health systems in managing cancer across different countries [305]. PTX is widely acknowledged as one of the most effective anti-cancer drugs developed in the past half-century and continues to be a primary treatment option for breast and ovarian cancers. However, the low concentration of PTX in natural *Taxus* species has necessitated various strategies to address supply challenges. Substantial advancements have been made in chemical and semi-chemical synthesis, direct extraction from *Taxus* cell lines, fermentation of PTX-producing endophytic fungi, and metabolic engineering aimed at enhancing PTX production in heterologous systems. Despite these efforts, PTX supply remains constrained. The recent elucidation of the PTX biosynthetic pathway has paved the way for metabolic engineering and synthetic biology approaches to improve PTX production in *Taxus* cell cultures or heterologous hosts such as *S. cerevisiae*. Researchers can now optimize the PTX biosynthetic gene set and its sequence to establish heterologous production systems, potentially transforming them into commercial production platforms. However, the PTX biosynthesis process generates numerous by-products. Additional research is required to identify more efficient biosynthetic routes and enhance the catalytic efficiency of each step. As a secondary metabolite,

PTX biosynthesis is regulated by a complex network, and the detailed regulatory mechanisms controlling PTX production in *Taxus* remain to be fully elucidated. This presents another challenge in addressing the low yield of PTX. Chemical synthesis also represents an important method for obtaining PTX. However, due to the structural complexity of PTX, industrial-scale total synthesis remains unlikely in the near future. Nevertheless, total synthesis can facilitate the discovery of more biologically relevant PTX analogs.

PTX serves a dual function in cancer therapy, both inducing tumor cell apoptosis through its established microtubule inhibition mechanism and enhancing tumor immunogenicity to activate the immune system against the tumor. While PTX has demonstrated significant efficacy in clinical chemo-immunotherapy, challenges persist, including low selectivity, high systemic toxicity, and limited induction of ICD. Nanocarrier systems have proven effective for PTX loading and targeting *in vivo*, due to their unique properties, such as high surface-to-volume ratios, nanoscale dimensions, biocompatibility, and extensive surface modifiability. Nanocarrier delivery systems loaded with PTX have emerged as promising therapeutic options in cancer treatment. However, while these systems have shown enhanced PTX solubility and therapeutic efficacy, further research is necessary before their widespread use in clinical trials. Challenges include controlling nanoparticle size and dispersity, elucidating drug release mechanisms *in vivo*, and mitigating the intrinsic toxicities of certain nanomaterials. To prevent severe allergic reactions induced by PTX, premedication with dexamethasone, diphenhydramine, cimetidine, and their analogs is routinely administered prior to chemotherapy. Additionally, peripheral neurotoxicity remains the most prevalent adverse reaction to PTX, limiting its clinical application. Chemoresistance presents another significant challenge that PTX treatment must address. Autophagy, considered a cellular self-protection mechanism, contributes to the development of drug resistance. PTX treatment can induce autophagy, activating autophagy marker [121]. Elucidating the mechanisms of drug resistance and overcoming this challenge will be a key focus of future research.

In conclusion, the persistent endeavors of global researchers have yielded substantial progress in the extraction, purification, and elucidation of PTX's anti-cancer mechanisms and nanocarrier systems. These advancements establish a robust foundation for the development of novel natural anti-tumor agents, potentially playing pivotal roles in enhancing human health and combating cancer in future therapeutic strategies.

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Declaration of competing interest

The authors declare no conflict of interest.

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The cover design illustrates the advancements in the resource, production, and clinical application. The forest background symbolizes the natural resource of paclitaxel. The human figure with a tumor, along with the infusion bag and tube, represents the clinical application of paclitaxel as an anti-cancer therapeutic, highlighting its delivery method for treating malignancies. Furthermore, the emphasized molecular structure of paclitaxel directly connects to the central theme of the article, underscoring the review's focus on the discovery and clinical application of this important compound. In summary, the cover employs symbolic visuals–yew tree forest, clinical delivery, and molecular structure–to align with the article's emphasis on paclitaxel's therapeutic journey against cancer.