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# Stimuli-responsive supramolecular hydrogels for paclitaxel delivery: Progress and prospects

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ABSTRACT

Cancer remains a leading cause of death worldwide, while chemotherapy playing a pivotal role in its management. However, traditional chemotherapy often encounters challenges such as non-specific drug delivery, systemic toxicity, and rapid clearance. Thermosensitive supramolecular hydrogels have emerged as an innovative platform for localized and sustained drug delivery, particularly for paclitaxel (PTX), a potent chemotherapeutic agent. These hydrogels exhibit unique sol-gel phase transitions at physiological temperatures, enabling minimally invasive administration and prolonged retention at tumor sites. Advances in hydrogel formulations, including dual stimuli-responsive systems and nanocrystal-loaded designs, enhance drug stability, controlled release, and therapeutic efficacy. Additionally, these hydrogels can incorporate multimodal therapeutic agents, such as immunomodulators and photosensitizers, achieving synergistic anticancer effects. Despite significant progress, challenges remain in optimizing tumor penetration, scaling production, and addressing tumor heterogeneity. Ongoing research into hydrogel composition, biocompatibility, and targeted delivery mechanisms aims to overcome these limitations, paving the way for their clinical translation. This review highlights recent advancements and future prospects of thermosensitive hydrogels for PTX delivery, emphasizing their potential to revolutionize cancer treatment by reducing systemic toxicity and improving localized therapeutic outcomes.

## 1. Introduction

Cancer remains one of the leading causes of death worldwide, presenting a profound global health challenge. According to the World Health Organization (WHO), cancer is the second leading cause of death globally, accounting for approximately 10 million deaths in 2020 (Wilkinson and Gathani, 2022a). The American Cancer Society's 2023 report highlights progress in early detection and treatment strategies, leading to declining mortality rates in some cancers, such as breast and colorectal cancer, particularly in high-income countries. However, these advancements are unevenly distributed, with significant disparities in low- and middle-income countries due to limited access to screening and treatment services (Bray et al., 2024; Klement, 2024; Wilkinson and Gathani, 2022b). The GLOBOCAN 2023 estimates underline a troubling rise in cases of lung, liver, and pancreatic cancers, which are often diagnosed at late stages and associated with poor prognoses (Jardim et al., 2023; Liu et al., 2024; Siegel et al., 2023).

Chemotherapy is a cornerstone of cancer treatment, yet its efficacy is hindered by challenges such as non-specific drug distribution, rapid clearance from circulation, and systemic toxicity (Amjad et al., 2024; Anand et al., 2023). Addressing these limitations, localized drug delivery systems have emerged as promising solutions, with thermosensitive hydrogels garnering significant attention (Lin et al., 2025; Omidian and Chowdhury, 2023). These hydrogels exhibit a unique sol-gel transition behavior, transitioning from a low-viscosity injectable solution at ambient temperature to a semi-solid gel depot at physiological temperatures (González-Garcinuño et al., 2024; Pardeshi et al., 2022; Tanga et al., 2023). This characteristic enables the localized and sustained release of anticancer agents at tumor sites, reducing systemic toxicity and improving therapeutic outcomes (Elumalai et al., 2024; Pacheco et al., 2023; Patel et al., 2024).

Taxanes, including PTX and docetaxel, play a pivotal role in cancer chemotherapy due to their potent anti-microtubule activity, targeting rapidly dividing cancer cells (Čermák et al., 2020; Maloney et al., 2020)

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Advances in taxane formulations have sought to overcome challenges like multidrug resistance and systemic toxicity (Lei et al., 2022; Jivani and Shinde, 2024). For instance, novel nanoparticle-based delivery systems, such as PTX-based PLGA-PEG-RhB, are being investigated for prostate cancer to minimize side effects and enhance drug (Deshmukh et al., 2024; Zhang et al., 2022). Additionally, alternative formulations such as oral PTX have shown promise in reducing systemic toxicity while maintaining therapeutic efficacy (Cheng et al., 2023; Mustafa et al., 2023). Research has also uncovered new insights into the biosynthesis pathways of taxanes, such as the role of previously unidentified CYP450 enzymes in PTX production, paving the way for more efficient production methods (Hossam Abdelmonem et al., 2024; Perez-Matas et al., 2023; Škubník et al., 2021).

Despite their efficacy, the clinical use of PTX is limited by poor aqueous solubility, rapid clearance, and systemic toxicity. Encapsulation of PTX in thermosensitive hydrogels offers a transformative approach to address these limitations (Wang et al., 2017; Xie et al., 2024; Zhai et al., 2024). Various hydrogel systems, including those based on gelatin derivatives, poloxamers, poly(ester-ether) copolymers, and bottlebrush copolymers, have been developed for sustained and targeted drug delivery (Qutub et al., 2024; Yuan et al., 2023). This review explores the advancements in thermosensitive hydrogel systems for delivering taxanes like PTX, emphasizing their role in improving cancer treatment outcomes and addressing the challenges associated with conventional chemotherapy.

## 2. Molecular mechanisms of PTX

### 2.1. Apoptosis induction mechanisms

PTX 's pro-apoptotic effects are primarily mediated through the stabilization of microtubules. By binding to β-tubulin, it prevents microtubule depolymerization (Fig. 1), disrupting the dynamic processes essential for mitotic spindle formation (Mukhtar et al., 2014; Wordeman and Vicente, 2021). This disruption causes mitotic arrest at the G2/M phase of the cell cycle, leading to cellular stress and activation of apoptotic pathways (Orth et al., 2012; Xu et al., 2013). The induction of apoptosis involves both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways. In the intrinsic pathway, PTX enhances the expression of pro-apoptotic proteins like Bax while suppressing anti-apoptotic proteins such as Bcl-2 (Apraiz et al., 2011; Peng et al., 2022). This imbalance triggers mitochondrial membrane permeabilization, leading to cytochrome *c* release and the activation of caspase-9 and downstream caspase-3, which orchestrate programmed cell death (Fig. 2) (Garrido et al., 2006; Guerrero et al., 2012). Simultaneously, the extrinsic pathway is activated through the upregulation of death receptors like Fas, amplifying the apoptotic response. These pathways often work synergistically, enhancing the effectiveness of PTX (Han et al., 2023; He et al., 2021a; Si et al., 2019)

Another critical mechanism in PTX -induced apoptosis is the generation of reactive oxygen species (ROS) (Cao et al., 2004; Redza-Dutordoir and Averill-Bates, 2016; Singh and Manna, 2022). By increasing oxidative stress within the cell, ROS damages cellular components and activates p53, a key tumor suppressor that promotes apoptosis. This oxidative damage further destabilizes mitochondrial integrity and facilitates the activation of caspase cascades (Jomova

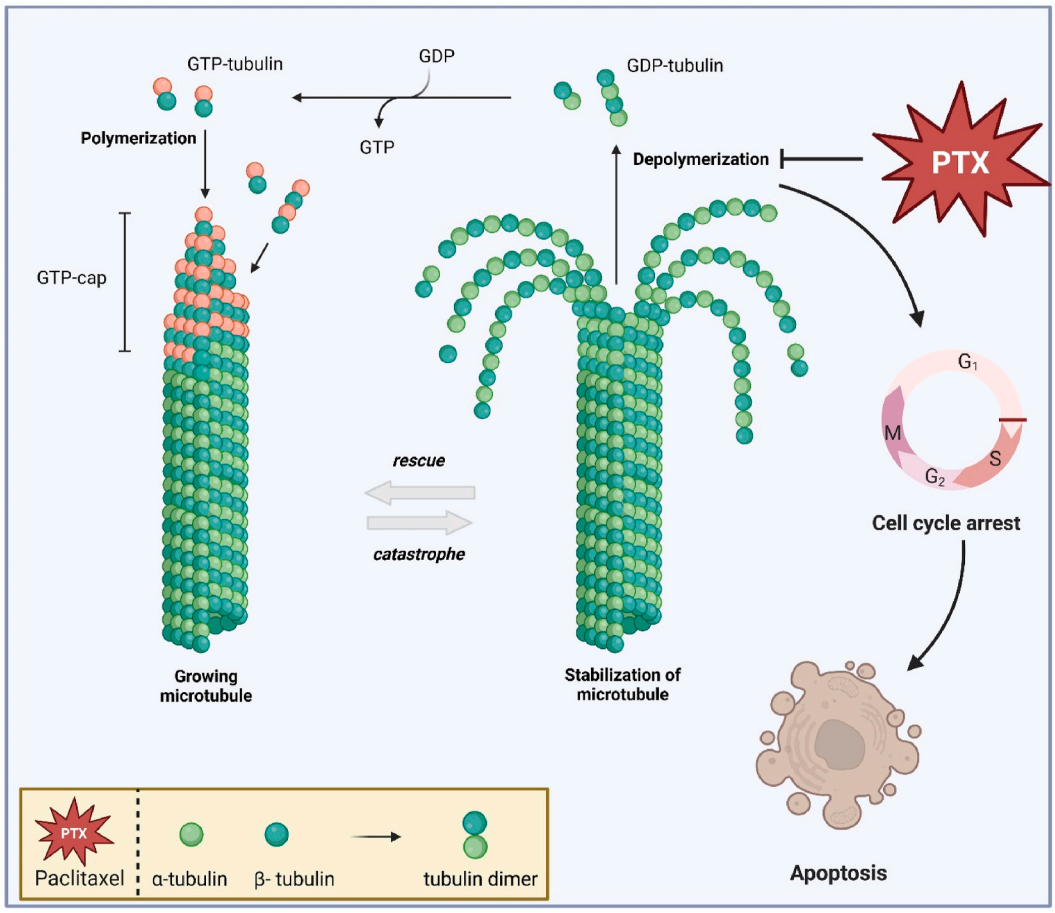


**Fig. 1.** Paclitaxel stabilizes microtubules, induces cell cycle arrest, and triggers apoptosis.

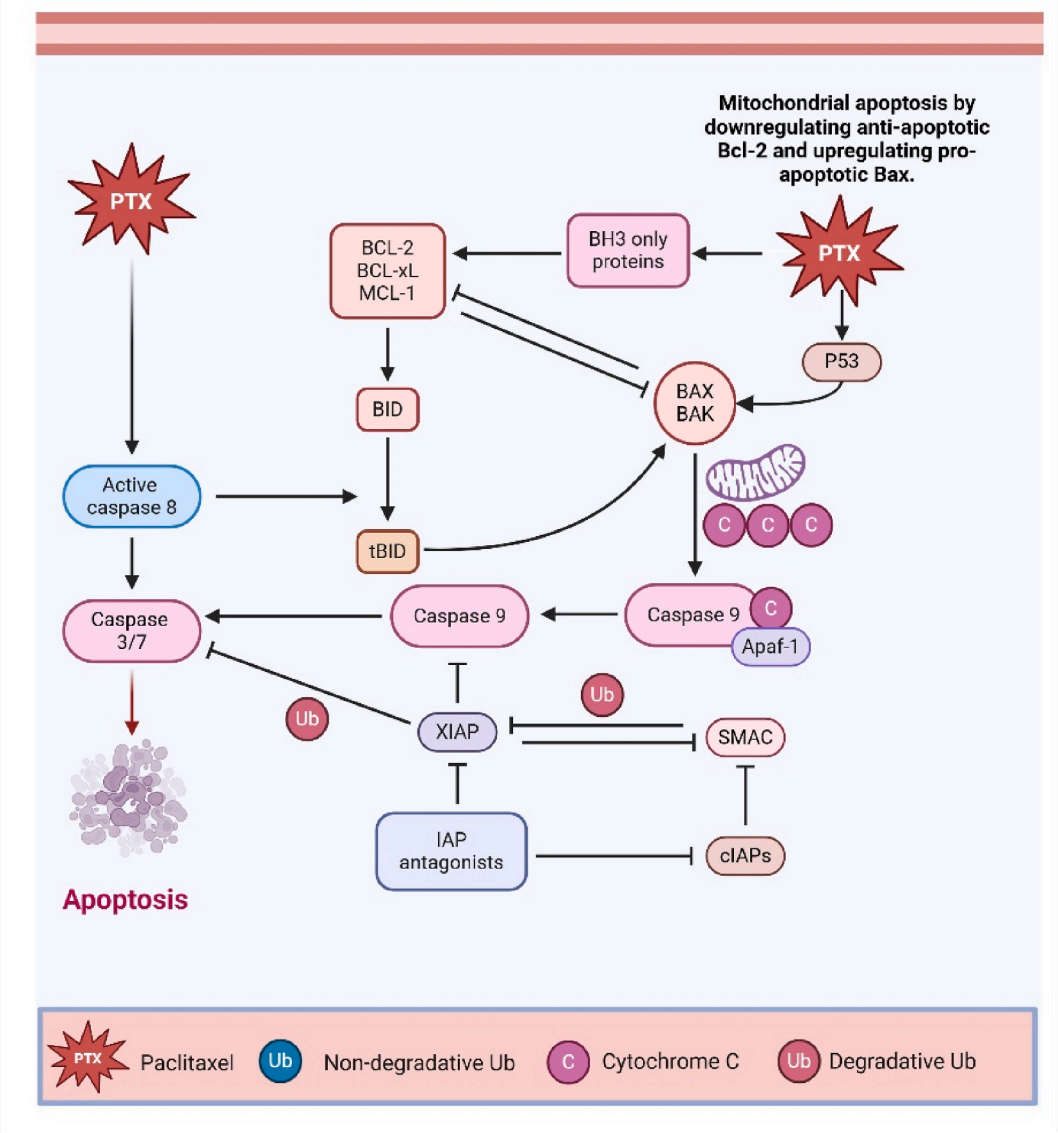


**Fig. 2.** Mechanism of paclitaxel-induced mitochondrial apoptosis pathway: Regulation of anti- and pro-apoptotic proteins.

et al., 2023; Rius-Pérez, 2023; Sharma et al., 2023). Caspase-dependent mechanisms play a central role in the execution of apoptosis, where effector caspase-3 cleaves structural and regulatory proteins, systematically dismantling the cell (Boice and Bouchier-Hayes, 2020; Hussar, 2022; Nguyen et al., 2021).

### 2.2. *Anti-proliferative mechanism*

In addition to inducing apoptosis, PTX exerts potent anti-proliferative effects by enforcing cell cycle arrest at the G2/M phase (Bruno et al., 2022; Wani et al., 2023). The stabilization of microtubules impairs the spindle assembly checkpoint, preventing mitosis and halting cell division (Musacchio, 2015). The stabilization of microtubules impairs the spindle assembly checkpoint, preventing mitosis and halting cell division (Foley and Kapoor, 2013). This process is reinforced by the accumulation of cyclin B1 and the inhibition of cyclin-dependent kinase 1 (CDK1) activity (Sakurikar et al., 2012). By disrupting the cell cycle, PTX effectively curtails the proliferative capacity of cancer cells (Hu et al., 2021). Beyond this, it inhibits key survival pathways, including PI3K/AKT and NF-κB, which cancer cells often exploit to evade apoptosis and sustain growth. The downregulation of these pathways further enhances PTX 's anti-proliferative effects, especially in resistant cancer types (Glaviano et al., 2023; He et al., 2021b; Long et al., 2024).

PTX also demonstrates a unique ability to sensitize resistant cancer cells to treatment. It modulates ATP-binding cassette (ABC) transporters, which are responsible for drug efflux, thereby enhancing the retention and efficacy of chemotherapeutic agents (Y. Fan et al., 2022; Giddings et al., 2021; Sun et al., 2012) This property makes PTX particularly valuable in combination therapies targeting multidrug-resistant tumors (Asnaashari et al., 2023; Kaveh Zenjanab et al., 2024; Sati et al., 2024). Furthermore, it exerts epigenetic effects by altering histone acetylation, leading to changes in gene expression that favor apoptosis and inhibit proliferation (Ozyerli-Goknar and Bagci-Onder, 2021; Wu et al., 2023). The drug also disrupts angiogenesis by targeting endothelial cells and inhibiting vascular endothelial growth factor (VEGF) signaling, depriving tumors of necessary nutrients and further suppressing growth (Elebiyo et al., 2022; Ghalehbandi et al., 2023).

## 3. Recent thermosensitive delivery systems for PTX delivery

Recent advancements in thermosensitive delivery systems for PTX focus on enhancing its anticancer efficacy through localized and sustained drug delivery (Haddad et al., 2022; Kortam et al., 2024).

Intelligent thermosensitive hydrogels have been developed to concentrate PTX's cytotoxic effects directly at tumor sites as shown in Fig. 3. (Chen et al., 2024; Xu et al., 2016). These systems utilize natural or synthetic gel-forming polymers to enable conformal administration into surgical cavities, prolonged intratumoral retention for weeks to months, and controlled release in response to endogenous stimuli (Lu et al., 2024a; Mashabela et al., 2022; Zhong et al., 2024). The platforms have been optimized for diverse cancer types, including brain, breast, and skin cancers, demonstrating efficacy in preclinical models.

The subsequent sections of the review examine the physicochemical properties, composition-structure-function relationships, drug release characteristics, and therapeutic efficacy of these systems as shown in Fig. 4, with an emphasis on their potential for clinical translation.

### 3.1. Dual (pH- and temperature-sensitive) gelatin based PTX hydrogels

Temperature- and pH-responsive gelatin-based hydrogels represent a novel and sophisticated modality for controlled drug delivery in oncology, leveraging their stimuli-responsive properties to optimize therapeutic efficacy and minimize off-target effects (Andrade et al., 2021; Lu et al., 2024b). These hydrogels exhibit a sol-to-gel phase transition under specific physiological conditions, enabling site-specific and sustained release of chemotherapeutic agents. In a study by Kang et al. (2021), oligosulfamethazine (OSM)-grafted gelatin hydrogels were engineered for the localized delivery of PTX to treat glioblastoma multiforme (GBM), an aggressive grade IV (forth) brain tumor with a median survival of 12–16 months. The OSM modification conferred dual pH and temperature sensitivity, facilitating controlled gel formation and drug release. The hydrogels demonstrated a retention of 63% of the PTX over 9 day at a tumor-relevant acidic pH of 6.5, effectively suppressing tumor progression in vivo in BALB/c mice, while maintaining biocompatibility (Kang et al., 2021). Similarly, Nieto et al. (2022) developed redox-responsive gellan gum-based hydrogels tailored for HER2-positive breast cancer. By fine-tuning the degree of crosslinking through buffer

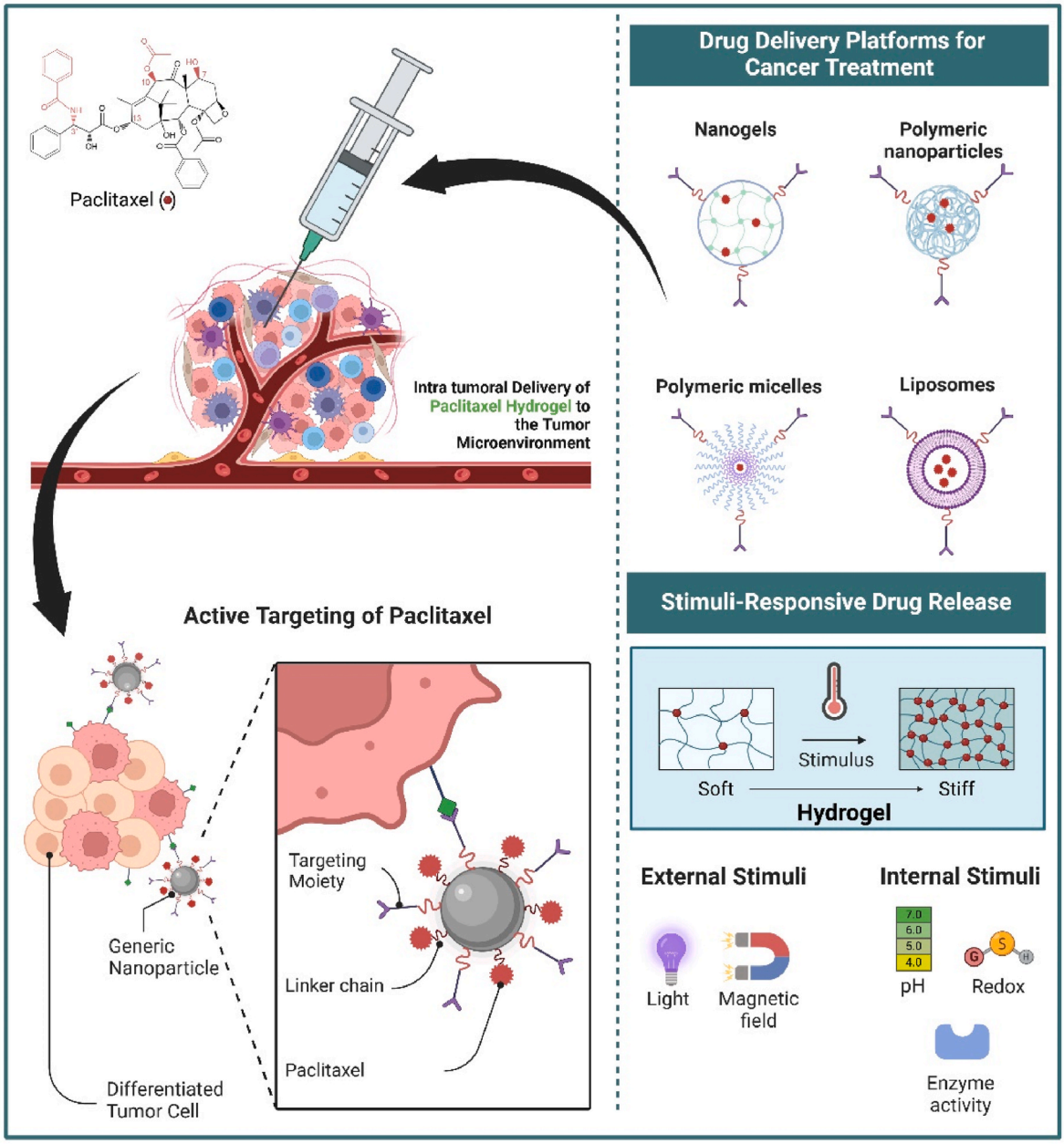


**Fig. 3.** Overview of drug delivery platforms and mechanisms for cancer treatment with paclitaxel (PTX).

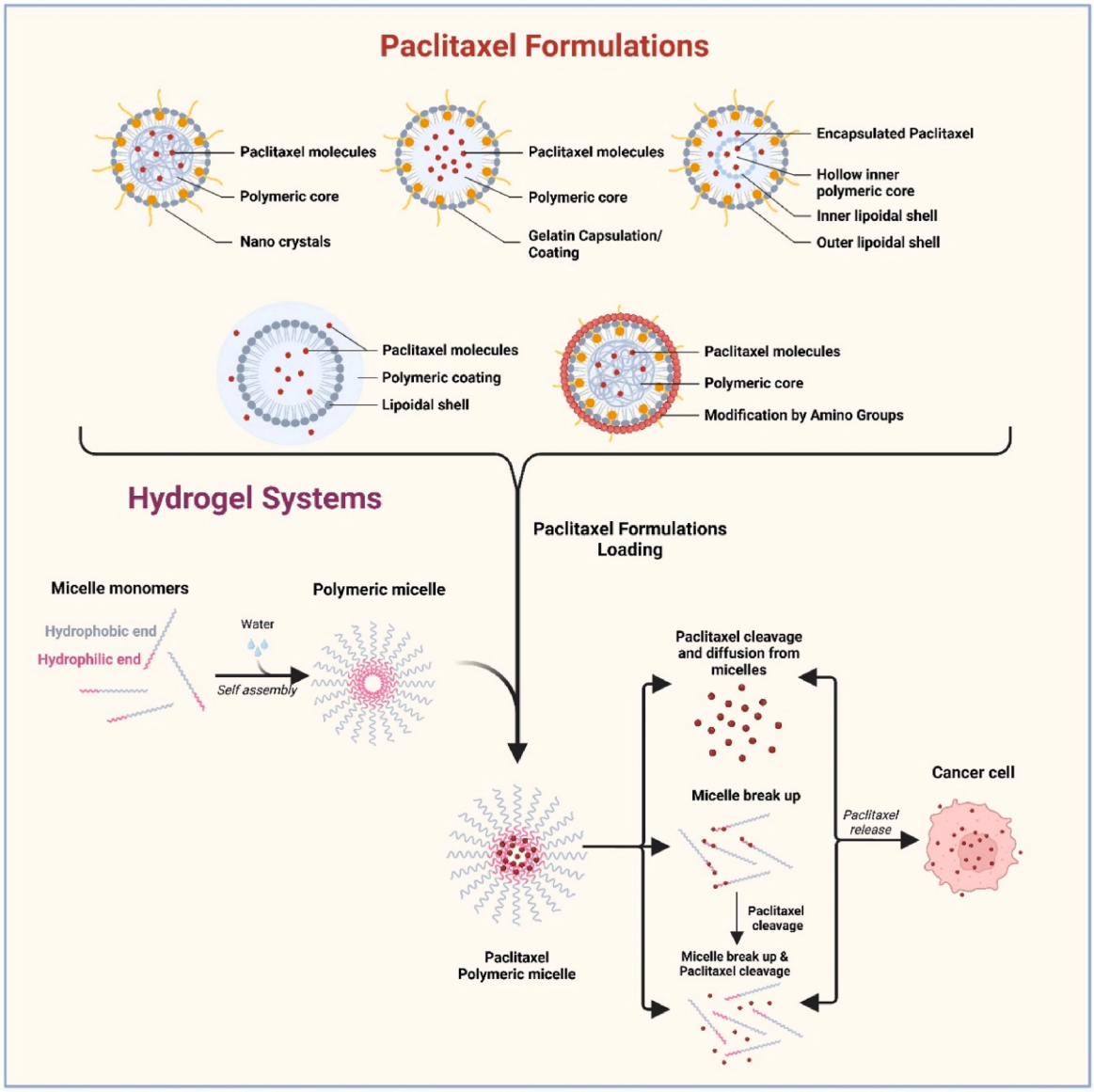


**Fig. 4.** Paclitaxel formulation: structural design, drug loading, and mechanisms of cancer cell targeting via hydrogel systems.

conditions and L-cysteine concentration, these hydrogels achieved glutathione-sensitive controlled release of PTX and exhibited significant antitumor activity in vitro, underscoring their potential for localized post-surgical chemotherapy (Nieto et al., 2022). Furthermore, Singh et al. (2014) explored injectable block copolymer hydrogels sensitive to both pH and temperature changes, demonstrating remarkable stability and sustained drug release capabilities suitable for diverse oncological applications(Singh and Lee, 2014). These investigations collectively highlight stimuli-responsive hydrogels' clinical potential as advanced drug delivery systems. Their ability to modulate drug release in response to the tumor microenvironment, reduce systemic toxicity, and enhance localized therapeutic impact underscores their transformative role in addressing the unmet needs of targeted cancer treatment.

### 3.2. *Nanocrystal-loaded thermosensitive PTX hydrogels*

PTX -loaded nanocrystals embedded within poloxamer-based thermosensitive hydrogels represent an innovative approach for enhancing localized cancer treatment (Guo et al., 2009; Voci et al., 2021). These systems demonstrate significant potential to address clinical challenges such as tumor recurrence and systemic toxicity by providing high drug-loading capacity, prolonged retention, and targeted delivery (Chung et al., 2020). The thermosensitive hydrogels utilize materials like poloxamer 407 and poloxamer 188, which enable rapid gelation at physiological temperatures, ensuring localized and sustained drug release (Chen et al., 2021).

Fan et al. (2022) developed a PTX nanocrystal thermosensitive hydrogel (PTX–NCS–gel) that gelates at 33.1 °C within minutes, offering enhanced viscoelasticity and self-recovery properties. In vitro studies showed controlled release and stability, while in vivo tests confirmed PTX–NCS–gel inhibited tumor recurrence and metastases in mouse model of postoperative breast cancer recurrence. Importantly, this system reduced adverse effects on the liver and spleen and provided a convenient application method directly into the surgical cavity (R. Fan et al., 2022b). Further supporting this approach, Gao et al. (2014) designed a hydrogel incorporating PTX nanocrystals (PTX-NCs), achieving a drug-loading capacity of 3 mg/ml. This formulation demonstrated prolonged retention within the tumor site, with over 10% of PTX retained 20 days post-injection in a murine 4T1 tumor model. The system exhibited sustained drug release, improved tumor tissue

accumulation, and lower systemic toxicity compared to Taxol®, while maintaining comparable cytotoxicity against cancer cells (Lin et al., 2014a). Khan et al. (2023) highlighted the application of PTX -loaded thermosensitive hydrogels for resistant cancers, highlighting efficient tumor accumulation and sustained efficacy in loco-regional applications (Khan et al., 2023). Moreover, Ju et al. (2013) synthesized a micelle-hydrogel hybrid system that optimized PTX solubility and release kinetics under tumor microenvironment conditions. This system exhibited prolonged tumor retention of 20 days, achieving a tumor inhibition rate with reduced toxicity compared to conventional formulations(Ju et al., 2013a).Similarly, Zhao et al. (2021) explored a PTX -niclosamide nanocrystal system embedded in a thermosensitive hydrogel for treating triple-negative breast cancer (TNBC), a particularly aggressive form of breast cancer. Their system exhibited controlled drug release over an 8-day period and demonstrated a tumor growth inhibition rate of 68.8%. Moreover, it reduced the proportion of breast cancer stem cells (BCSCs), which are associated with tumor recurrence and metastasis (Zhao et al., 2021).

Collectively, these findings underscore the therapeutic potential of PTX nanocrystal-loaded thermosensitive hydrogels as advanced drug delivery systems. By improving localized retention, enhancing drug synergy, and minimizing systemic side effects, these systems represent a promising step forward in oncological therapies.

### 3.3. Microspheres and cisplatin based thermosensitive PTX hydrogels

The incorporation of PTX and cisplatin microspheres into thermosensitive hydrogels represents a promising approach for localized, sustained drug delivery, addressing several challenges in oncology, such as systemic toxicity and inefficient drug targeting (Gupta et al., 2024). This dual-drug system utilizes the distinct properties of microspheres and thermosensitive hydrogels to ensure controlled drug release and prolonged therapeutic efficacy(Esmaeili et al., 2021). In the study by Mittal et al. (2011), the combination of PTX and carboplatin microspheres embedded in a biodegradable thermosensitive hydrogel was developed to achieve sustained drug release. The system demonstrated a synchronized drug release profile, with PTX exhibiting a biphasic release over 50–60 days, while carboplatin was released with an initial burst of 40–50%. This burst release was effectively controlled by encapsulating carboplatin in poly(L-lactide) microspheres, which were then dispersed in the PTX -loaded hydrogel. This novel formulation reduced the burst release associated with conventional systems and allowed for the simultaneous, sustained release of both drugs, which could be further explored for solid tumor treatment (Mittal et al., 2011).

Liu et al. (2023) developed a hydrogel system co-loaded with porous PTX -loaded polylactide microspheres and cisplatin, offering a dual-drug delivery platform that significantly enhanced anticancer efficacy. The system demonstrated sustained release, with prolonged drug retention and improved tumor penetration. In vivo studies showed that the dual-drug system inhibited tumor growth, prolonged the survival of tumor-bearing mice, and exhibited no major toxic effects on vital organs. Immunohistochemical analysis revealed significant tumor cell proliferation inhibition and induced apoptosis, further suggesting the therapeutic potential of this dual-drug hydrogel system (Liu et al., 2023).

In the treatment of peritoneal carcinomatosis associated with gastric cancer, Han et al. (2017) utilized thermosensitive hydrogels loaded with PTX and cisplatin, which improved drug accumulation in the tumor and reduced side effects compared to conventional chemotherapy. Zhao et al. (2021) introduced a similar strategy for the treatment of triple-negative breast cancer (TNBC), combining PTX nanocrystals with niclosamide in a thermosensitive hydrogel. This formulation showed synergistic effects, with an in vivo tumor growth inhibition rate of approximately 68.8%, and significantly suppressed breast cancer stem cells, which could potentially prevent recurrence and metastasis in TNBC (Han et al., 2017).

Ju et al. (2013) and Liang et al. (2018) explored the potential of thermosensitive hydrogels for targeting the tumor microenvironment. They demonstrated that systems like micelle-hydrogel hybrids and carboplatin-loaded hydrogels could enhance drug delivery in acidic and hypoxic conditions, optimizing therapeutic outcomes. These systems not only minimized toxicity but also maintained therapeutic efficacy, especially in the treatment of glioma and other challenging tumor types (Ju et al., 2013b; Liang et al., 2018).

Xiao et al. (2022) further expanded on the application of thermosensitive hydrogels for intraperitoneal chemotherapy, demonstrating that a hydrogel loaded with norethindrone nanoparticles and oxaliplatin effectively inhibited ascites formation in hepatocellular carcinoma (HCC). The system induced significant apoptosis in tumor cells, reduced tumor cell proliferation, and improved survival in animal models, further supporting the therapeutic potential of thermosensitive hydrogel-based chemotherapy platforms (Xiao et al., 2022).

These studies highlight significant advancements in localized chemotherapy through the use of thermosensitive hydrogels, which offer controlled and sustained drug release. This approach enhances tumor targeting while minimizing systemic toxicity, ultimately improving the therapeutic outcomes. Furthermore, dual-drug systems, such as those explored by Xiao et al. (2022), are proving to be particularly beneficial in overcoming drug resistance. By combining two therapeutic agents, these systems not only enhance efficacy but also provide a more comprehensive treatment strategy for metastatic cancer, addressing key challenges in conventional chemotherapy.

### 3.4. Nanosuspension based thermosensitive PTX hydrogels

The integration of PTX nanosuspensions into thermosensitive hydrogels has emerged as a promising strategy for enhancing localized chemotherapy, improving bioavailability, and reducing systemic toxicity (Ma et al., 2023; Pei et al., 2023). This approach is supported by several studies exploring its application across different cancer types, with significant findings in both therapeutic efficacy and drug delivery. Lu et al. (2022) investigated the combination of PTX with honokiol nanosuspensions in thermosensitive hydrogels for breast cancer treatment. The developed system demonstrated superior gelation properties and effective tumor targeting, with an impressive tumor inhibitory rate of 72.51% in vivo. The localized administration of PTX, coupled with the slow, sustained release of honokiol from the hydrogel, facilitated prolonged drug retention and enhanced therapeutic effects. The study highlighted that such localized drug delivery not only improved tumor accumulation but also promoted synergistic cytotoxicity, enhancing overall treatment response (Lu et al., 2022). These findings suggest that this system could significantly enhance the efficacy and safety of PTX-based therapies in treating breast cancer. This points to the potential of such formulations not only in treating the primary tumor but also in preventing relapse and metastasis, addressing a significant challenge in TNBC therapy.

For bladder cancer, Sun et al. (2018) designed a chitosan-based thermosensitive hydrogel containing PTX nanosuspensions for intravesical drug delivery. This formulation exhibited sustained drug release for over 10 days, significantly improving therapeutic efficacy in an intravesical bladder cancer model. The positively charged PTX/chitosan nanosuspensions ensured effective adhesion to the bladder mucosa, enhancing drug retention and bioavailability. This system not only improved drug accumulation at the cancer site but also reduced systemic toxicity, a critical factor in cancer therapy (Liu et al., 2018).

The studies highlight the significant potential of PTX nanosuspensions integrated into thermosensitive hydrogels for localized chemotherapy. These systems offer controlled, sustained release, improved tumor targeting, and reduced systemic toxicity, making them particularly effective in treating aggressive and recurrent cancers. Future research should focus on optimizing these formulations for broader clinical applications, with a particular emphasis on personalized

medicine and the treatment of various cancer subtypes.

### 3.5. Amino-modified thermosensitive PTX hydrogels

The development of amino-modified thermosensitive hydrogels as drug delivery systems has gained significant attention due to their potential to improve therapeutic efficacy, reduce systemic toxicity, and offer localized and controlled release of drugs such as PTX. These advanced platforms integrate smart polymer technology to respond to physiological stimuli, offering unique advantages for cancer treatment. Shaibie et al. (2023) study focused on thermoresponsive hydrogels based on poly(N-isopropylacrylamide) (PNIPAAm), modified with amino groups to enhance the delivery of PTX. PNIPAAm's low critical solution temperature (LCST) of approximately 32 °C, close to human body temperature, makes it particularly suitable for pharmaceutical applications. The research demonstrated that the hydrogel undergoes a temperature-sensitive phase transition at 37 °C, enabling precise control over drug release. Furthermore, the film hydration method employed for drug encapsulation minimized burst release and prolonged the delivery duration (Shaibie et al., 2023a). The versatility of PNIPAAm extends beyond drug delivery; it is also utilized in biomedical applications like cell culture media and chromatography systems (Shaibie et al., 2023b; Throat and Bhattacharya, 2024). By copolymerizing PNIPAAm with hydrophobic or hydrophilic molecules, its LCST and properties can be tailored for specific therapeutic needs (Safakas et al., 2021; Zhang et al., 2010). The findings underscore PNIPAAm's status as a robust "smart polymer" in pharmaceutical science, opening doors for further exploration of its applications.

Building on the utility of thermosensitive hydrogels, Feng et al. (2020) developed injectable systems supported by PEGylated amino-modified polycaprolactone (PCL) nanoparticles. The synthesized PECN15 triblock copolymers showed an optimal amino group content, facilitating improved intracellular drug delivery. The PTX-loaded nanoparticles demonstrated sustained drug release over 10 days and significantly reduced IC50 values compared to traditional formulations. The study highlighted the hydrogels' ability to respond to the acidic environment of endosomes, ensuring enhanced drug uptake and release efficiency. The therapeutic results were striking, with a tumor growth inhibition rate of 94.27% following peritumoral injection, outperforming both standard PTX formulations and previous hydrogels (Guo et al., 2020; Luckanagul et al., 2021). This demonstrates the potential of amino-modified systems to revolutionize cancer treatment by optimizing drug targeting and minimizing adverse effects.

These studies emphasize the transformative role of amino-modified thermogels in cancer therapy, particularly in delivering hydrophobic drugs like PTX. The incorporation of PNIPAAm and PCL polymers allows for fine-tuned drug release and reduced systemic toxicity. While both Shaibie et al. and Feng et al. provide robust evidence for the effectiveness of these hydrogels, their approaches differ in polymer selection and gelation mechanisms, reflecting the flexibility of design inherent to these systems.

The findings also invite discussions on scalability and long-term safety. While the enhanced biocompatibility and localized delivery are promising, further research is needed to explore the impact of prolonged use and the potential for polymer degradation products to elicit adverse effects. Moreover, functionalizing these hydrogels with targeting ligands or immune-modulating agents could expand their utility, as suggested by the reactivity of amino groups in Feng et al.'s work.

## 4. Limitations of PTX thermosensitive hydrogel systems in cancer treatment

Thermosensitive hydrogel systems for delivering PTX represent a significant innovation in localized cancer therapy. These hydrogels are designed to transition from a liquid state at low temperatures to a gel state at body temperature, enabling localized, sustained release of PTX. Despite their potential to minimize systemic toxicity and improve drug concentration at the tumor site, these systems face several limitations that challenge their effectiveness and clinical translation.

### 4.1. Limited tumor penetration

One significant limitation is the restricted ability of these hydrogel systems to penetrate the tumor microenvironment effectively (Andrgie and Tsai, 2024; Li et al., 2023a). Tumors are characterized by a dense extracellular matrix (ECM) that can impede the diffusion of PTX from the hydrogel into deeper tumor tissues (Li et al., 2022; Tamayo-Angorrilla et al., 2022). As a result, the drug may not reach all cancer cells uniformly, leading to suboptimal therapeutic outcomes. This limited penetration is particularly problematic in solid tumors with poor vascularization or significant fibrosis, which further hinder drug diffusion (Raza et al., 2023; Seynhaeve et al., 2020).

### 4.2. Challenges in controlled drug release

Achieving a consistent and controlled release profile is critical for the success of hydrogel-based systems (Liu and Chen, 2024). However, factors such as the degradation rate of the hydrogel matrix, PTX 's physicochemical properties, and local environmental conditions (e.g., pH and temperature) can result in uneven drug release (Vasile et al., 2020; Xu et al., 2017). A common issue is the "burst release" phenomenon, where a large portion of the drug is released rapidly upon hydrogel implantation (Raina et al., 2022; Yoo and Won, 2020). This sudden release can lead to localized toxicity, damaging surrounding tissues, and may reduce the duration of therapeutic efficacy (Thang et al., 2023). Conversely, if drug release is too slow or incomplete, the desired therapeutic dose may not be achieved, undermining treatment efficacy.

### 4.3. Immune and inflammatory reactions

The biocompatibility of thermosensitive hydrogels is crucial for their successful application. However, certain synthetic polymers such as PNIPAAm used in these systems may trigger immune responses or local inflammation (R. Fan et al., 2022a; Huang et al., 2019). This inflammatory reaction can alter the tumor microenvironment, potentially promoting cancer cell resistance to PTX or hindering its effectiveness. Furthermore, persistent inflammation might lead to adverse effects such as tissue damage or pain at the implantation site, complicating patient management (Hibino et al., 2021; Kartikasari et al., 2021; Tan et al., 2021).

### 4.4. Tumor heterogeneity and microenvironment variability

The heterogeneity of tumors presents another challenge for PTX hydrogel systems. Variations in tumor vasculature, ECM composition, and cellular metabolism can influence how the hydrogel and its drug payload interact with the tumor (Awad et al., 2023; Fan et al., 2023; Solanki and Bhatia, 2024). For example, hypoxic or acidic tumor regions can accelerate hydrogel degradation, potentially altering PTX release profiles. Poorly vascularized regions may further limit drug diffusion and uptake by cancer cells, reducing therapeutic impact (Chehelgerdi et al., 2023; Zhang et al., 2021).

### 4.5. Difficulties in manufacturing and scalability

Producing thermosensitive hydrogels with consistent quality and performance is a complex process. The precise control of polymer composition, molecular weight, and cross-linking density is essential to ensure reliable drug release and gel formation (Ahmed, 2015; El Sayed, 2023). Scaling up these systems for widespread clinical use poses additional challenges, such as maintaining batch-to-batch consistency,

sterility, and cost-effectiveness. These manufacturing hurdles can delay commercialization and increase overall development costs (Đorđević et al., 2022; Sampathkumar and Kerwin, 2024).

### 4.6. Ineffectiveness against metastatic cancers

While thermosensitive hydrogels are effective for localized drug delivery, they are less suitable for treating metastatic cancers (Al Sabbagh et al., 2020; Fan et al., 2019). Metastatic disease often requires systemic drug distribution to target distant tumor sites (Ganesh and Massagué, 2021). Since hydrogels are confined to the site of application, their use is limited to localized primary tumors or accessible metastases, making them less effective for advanced-stage or widely disseminated cancers (Correa et al., 2021).

## 5. Potential therapeutic implications of thermosensitive PTX hydrogel systems in cancer treatment

PTX has shown enhanced efficacy when delivered through thermosensitive hydrogel systems. These hydrogels, which transition from liquid to gel at physiological temperatures, provide localized, controlled, and sustained release of drugs, addressing limitations associated with conventional chemotherapy such as systemic toxicity and rapid drug clearance. Below, we discuss the therapeutic benefits and implications of this novel delivery approach.

Thermosensitive hydrogels loaded with PTX significantly enhance drug retention at the tumor site (Cirillo et al., 2019; Mao et al., 2016). These hydrogels form a semi-solid depot post-injection, ensuring a localized release of PTX over extended periods. Studies have demonstrated that this approach minimizes systemic drug distribution, reducing toxicity to normal tissues while maintaining high drug concentrations within the tumor microenvironment (Ma et al., 2022; Wei et al., 2020). This characteristic is particularly advantageous for post-surgical applications, such as in breast cancer, where recurrence often stems from residual microscopic disease. The sustained release of PTX from thermosensitive hydrogels prolongs its cytotoxic effects on proliferating cancer cells (Li et al., 2024; Yu et al., 2024). Thermosensitive hydrogels provide a targeted approach, limiting drug exposure to healthy tissues (Li et al., 2023b; Ma and Yan, 2021). A thermosensitive hydrogel containing PTX significantly reduced systemic toxicity in preclinical models while maintaining its therapeutic efficacy (Lin et al., 2014b).

The composition of thermosensitive hydrogels can be tailored to achieve specific release profiles (Li and Mooney, 2016). Advances in hydrogel technology, such as the incorporation of nano delivery, enable precise control over drug release kinetics (Kass and Nguyen, 2022). For example, PTX -loaded liposomal hydrogels demonstrated both improved stability and enhanced permeability, making them ideal for in situ delivery in pancreatic cancer (Indolfi et al., 2016; Kakinoki et al., 2007). Thermosensitive hydrogels serve as versatile platforms for integrating chemotherapy with other treatment modalities. Hydrogels co-loaded with PTX and photosensitizers or gene therapy agents have been successfully employed in multimodal approaches to cancer treatment (Gan et al., 2023). This versatility broadens the therapeutic spectrum and enhances treatment efficacy for complex cancers.

## 6. Conclusion

The integration of PTX into hydrogel systems represents a transformative approach to overcoming the limitations of conventional chemotherapy. These innovative delivery platforms leverage the unique properties of hydrogels, such as stimuli-responsiveness and sol-gel transitions, to provide localized, controlled, and sustained drug release at tumor sites. By reducing systemic toxicity and enhancing drug retention, hydrogels optimize the therapeutic efficacy of PTX, making them particularly valuable in treating solid tumors and preventing recurrence. Recent advancements, including dual-responsive systems and nanocrystal-loaded hydrogels, have further refined the precision and efficiency of PTX delivery. These systems address critical challenges, such as poor solubility and multidrug resistance, while offering the flexibility to incorporate additional therapeutic agents for synergistic effects.

Despite significant progress, challenges remain in hydrogel design and application. Limited tumor penetration, manufacturing scalability, and variability in tumor microenvironments are key hurdles that require continued research and innovation. Strategies to enhance biocompatibility, tailor hydrogel properties to individual tumor profiles, and incorporate advanced drug delivery mechanisms will be essential for clinical translation.

## CRediT authorship contribution statement

**Mohammad Qutub:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Amol Tatode:** Writing – review & editing, Writing – original draft, Supervision. **Jayshree Taksande:** Writing – review & editing, Writing – original draft, Conceptualization. **Tanvi Premchandani:** Writing – review & editing, Writing – original draft, Conceptualization. **Milind Umekar:** Writing – review & editing, Writing – original draft. **Ujban Md Hussain:** Writing – review & editing, Visualization. **Dinesh Biyani:** Writing – review & editing. **Dadaso Mane:** Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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