# NANOPARTICLE-BASED DOXORUBICIN DELIVERY SYSTEMS FOR IMPROVED CANCER TREATMENT

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## Abstract

Chemotherapy, especially doxorubicin, is a key component of treatment for cancer, which continues to be a major cause of morbidity and death globally. Dose-dependent toxicities, including as cardiotoxicity, myelosuppression, and the emergence of drug resistance, restrict the therapeutic usage of doxorubicin despite its strong anticancer efficacy. By improving solubility, stability, and bioavailability while permitting targeted administration to tumor regions, nanoparticle-based delivery systems have emerged as a viable approach to get around these restrictions. When compared to free doxorubicin, a number of platforms, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, micelles, and dendrimers, have shown better pharmacokinetics, greater tumor accumulation, and decreased systemic toxicity. To guarantee the best possible therapeutic results, these nanoparticles must be thoroughly characterized in terms of their size, shape, surface charge, drug loading, and release kinetics. Preclinical research has demonstrated that doxorubicin encapsulated in nanoparticles increases cytotoxicity against cancer cells, more successfully slows tumor development, and reduces off-target effects. To achieve synergistic anticancer effects, these systems can also be combined with combination therapies like radiation or immunotherapy. Despite their potential, there are still issues with large-scale production, safety assessment, regulatory approval, and customized application, which emphasizes the necessity of ongoing research and development. All things considered, doxorubicin delivery systems based on nanoparticles present a potent strategy to enhance the safety and effectiveness of chemotherapy, opening the door to more accurate, efficient, and patient-friendly cancer treatments.

**Keywords:** *Doxorubicin, Nanoparticles, Cancer therapy, Targeted drug delivery, Liposomes, Polymeric nanoparticles*

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## 1. INTRODUCTION

Due to its substantial morbidity and death, cancer remains a major global public health concern. Over 19 million new cases were diagnosed worldwide in 2023, according to recent predictions, and the burden is expected to rise as a result of lifestyle risk factors like smoking, obesity, and environmental exposures as well as population aging (Ferlay et al., 2024). Chemotherapy is still a cornerstone of cancer treatment, especially for advanced or metastatic disease. Anthracycline antibiotics, like doxorubicin, are frequently used because of their strong cytotoxic mechanisms, which include intercalation into DNA strands, inhibition of topoisomerase II activity, and production of reactive oxygen species (ROS), which cause rapidly dividing cancer cells to undergo apoptosis ((Minotti et al., 2023).

The use of doxorubicin is severely restricted by dose-dependent toxicities, despite its therapeutic usefulness across a variety of cancers. The most worrisome side effect is still cardiotoxicity, which can be fatal and include asymptomatic drops in left ventricular ejection fraction, arrhythmias, and congestive heart failure (Yeh et al., 2023). Myelosuppression, mucositis, alopecia, and gastrointestinal problems are additional systemic toxicities that impair patient quality of life and may require dosage decrease or treatment cessation (Konieczny et al., 2022). Furthermore, doxorubicin's therapeutic effectiveness is gradually reduced by the emergence of multidrug resistance (MDR) in cancer cells, which is caused by efflux transporters such P glycoprotein, improved DNA repair pathways, and modified apoptotic signals ((Szakacs et al., 2021).

Drug delivery systems based on nanotechnology have become a viable way to overcome these constraints. Doxorubicin can be encapsulated in nanoparticles, which are usually between 10 and 200 nm in diameter. This protects the drug against quick breakdown, increases its water solubility, and modifies its pharmacokinetic behavior (Blanco et al., 2022). Because of leaky endothelial junctions and inadequate lymphatic drainage, the tumor vasculature's enhanced permeability and retention (EPR) effect enables nanoparticles to preferentially accumulate within the tumor interstitium, increasing local drug concentration and decreasing systemic exposure (Maeda & Khatami, 2020). Active targeting techniques go beyond passive targeting by functionalizing the surface of nanocarriers with ligands (such as antibodies, peptides, or folate) that identify tumor-specific receptors. This allows for receptor-mediated endocytosis and enhanced absorption by cancer cells (Danhier et al., 2022).

In comparison to free doxorubicin, preclinical research has shown that doxorubicin-loaded nanoparticles can greatly enhance pharmacokinetic characteristics and biodistribution, leading to higher tumor drug concentrations and noticeably lower cardiotoxicity (Sinha et al., 2022). Additionally, each of these nanocarrier platforms—polymeric nanoparticles, liposomes, solid lipid nanoparticles, micelles, and dendrimers—offers special benefits, including enhanced circulation time, high drug loading, controlled or stimuli-responsive drug release, and opportunities for multifunctional design, making them potent instruments for precision oncology (Danhier et al., 2022; Blanco et al., 2022). All of these developments point to the possibility of using nanoparticle-based systems to improve the safety and efficacy of conventional chemotherapy.

## 2. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

By modifying the drug's physicochemical characteristics, nanoparticle-based drug delivery systems aim to improve drug delivery. Nanoparticles can be engineered to target cancer cells specifically, improve solubility, control medication release, and get past biological barriers.

### 2.1 TYPES OF NANOPARTICLES FOR DOXORUBICIN DELIVERY

Doxorubicin (DOX) can now be delivered more effectively thanks to a variety of nanoparticle platforms that improve drug stability, targeting, controlled release, and lower systemic toxicity. Every kind of nanoparticle has unique biological and physicochemical characteristics that can be modified for certain therapeutic uses in the treatment of cancer (Yetisgin et al., 2020).

- **Polymeric Nanoparticles**: Colloidal carriers known as polymeric nanoparticles are created from biodegradable and biocompatible polymers such chitosan, polycaprolactone, and polylactic-co-glycolic acid (PLGA) (Begines et al., 2020). In order to minimize quick clearance and systemic toxicity while maintaining therapeutic medication levels in the tumor, these polymers can be designed to produce controlled and prolonged drug release. For instance, PLGA nanoparticles improve bioavailability and lessen off-target effects by shielding encapsulated DOX from premature breakdown and releasing the medication gradually over time (Alsaab et al., 2022). Chitosan is a naturally occurring polysaccharide that provides mucoadhesive qualities and can improve cellular absorption, which makes it appealing for the construction of nanoparticles.
- **Liposomes**: Liposomes are spherical vesicles with one or more phospholipid bilayers that can contain hydrophobic medications inside the bilayer and hydrophilic drugs in

the aqueous core (Abbasi et al., 2022). Clinically approved liposomal doxorubicin formulations, such as PEGylated liposomal DOX (e.g., Doxil®), have shown improved tumor accumulation through the enhanced permeability and retention (EPR) effect, prolonged circulation time, and decreased cardiotoxicity. Stability and tumor selectivity are further enhanced by surface modification using targeted ligands or polyethylene glycol (PEG).

- **Solid Lipid Nanoparticles (SLNs)**: Compared to traditional emulsions, SLNs offer improved physical stability and controlled release since they are made of solid lipid matrices that stay solid at body temperature. SLNs enhance oral or parenteral distribution, shield integrated DOX against deterioration, and can be scaled up for production using very straightforward procedures (Puri et al., 2009). To further improve medication loading and release kinetics, variations like nanostructured lipid carriers (NLCs) combine liquid and solid lipids.
- **Micelles**: In watery conditions, amphiphilic block copolymers generate micelles, which are self-assembling nanoparticles. They have a hydrophilic shell that keeps the micelle stable in biological fluids and a hydrophobic core that can dissolve poorly water-soluble medications like DOX (Hsu et al., 2023). To take advantage of variations in the tumor microenvironment for triggered drug release, polymeric micelles can be designed to be stimuli responsive (e.g., pH or redox sensitive) (Yu et al., 2024).
- **Dendrimers**: High drug loading and precise surface modification are made possible by dendrimers, which are highly branched, monodisperse macromolecules with many surface functional groups. These characteristics improve tumor selectivity and circulation time by facilitating the coupling of DOX with targeted moieties. In preclinical research, PEGylated dendrimers have demonstrated enhanced DOX pharmacokinetics and decreased systemic toxicity (ud Din et al., 2017).

**Table 1: Therapeutic Outcomes of Doxorubicin-Loaded Nanoparticles**

| Nanoparticle Type | Cancer Model | Key Findings | Effect on Toxicity |
|---|---|---|---|
| Liposomal Doxorubicin | Breast cancer xenograft | Higher tumor accumulation, slower tumor growth | Reduced cardiotoxicity |
| Polymeric Micelles | Liver cancer cells (in vitro & in vivo) | Enhanced apoptosis, improved cellular uptake | Minimal systemic toxicity |

| | | | |
|---|---|---|---|
| Solid Lipid Nanoparticles | Lung cancer xenograft | Sustained drug release, improved tumor inhibition | Reduced off-target toxicity |
| Dendrimer-Conjugated Doxorubicin | HER2+ breast cancer | Targeted delivery via ligand, improved tumor regression | Limited cytotoxicity in normal cells |
| PEGylated Nanoparticles | Murine melanoma model | Extended circulation, higher tumor accumulation | Reduced systemic side effects |

## 2.2 NANOPARTICLE DESIGN FOR TARGETED DELIVERY

To maximize therapeutic efficacy while reducing systemic toxicity, nanoparticles must be designed for targeted administration. Passive targeting and active targeting are the two main tactics used. Both strategies selectively deliver therapeutic payloads to cancer cells by taking advantage of particular physiological and molecular characteristics of malignancies.

### 2.2.1 Passive Targeting via the EPR Effect

The Enhanced Permeability and Retention (EPR) effect, which is seen in many solid tumors, is exploited by passive targeting. Rapid angiogenesis causes broad fenestrations and leaky blood vessels, which make tumor vasculature often uneven, disorganized, and extremely permeable. Furthermore, tumors frequently have poor lymphatic drainage, which hinders the effective removal of macromolecules and nanoparticles (Maeda, 2015).

These holes in the tumor vasculature allow nanoparticles, which are usually between 10 and 200 nm in size, to extravasate more easily than in healthy tissues and stay in the tumor interstitium (Zhang et al., 2017). This selective accumulation improves the therapeutic index and lowers systemic side effects by increasing local drug concentration in the tumor while lowering exposure to healthy organs. Many clinically effective nanomedicines, including PEGylated liposomal doxorubicin formulations, are based on the EPR effect (Iyer et al., 2006).

However, due to variations in vascular permeability and microenvironment, the EPR effect's amplitude can differ between patients and tumor types, prompting researchers to supplement passive targeting with other tactics (Prabhakar et al., 2013).

### 2.2.2 Active Targeting

Functionalizing the surface of nanoparticles with particular ligands that can identify and attach to overexpressed receptors on cancer cells is known as active targeting. By promoting receptor-mediated endocytosis, increasing cellular uptake of the drug-loaded nanoparticle, and minimizing off-target effects, this strategy improves targeting specificity.

Common ligands used for active targeting include:

- **Antibodies and antibody fragments:** These can be made to identify antigens unique to tumors, including HER2 (Human Epidermal Growth Factor Receptor 2), which is overexpressed in some types of breast cancer (Park *et al.*, 2016).
- **Peptides:** By targeting integrins on tumor vasculature and cancer cells, small peptides such RGD (arginine glycine aspartic acid) improve selective binding (Ruoslahti, 2017).
- **Small molecules:** To target folate receptors, which are increased in a number of malignancies, including lung and ovarian tumors, folate (vitamin B9) can be conjugated to nanoparticles (Sudimack & Lee, 2000).
- **Transferrin:** Transferrin ligand functionalization can enhance targeting through transferrin receptor binding since many tumor cells have a high iron demand (Daniels *et al.*, 2012).

Multifunctional nanoparticles can potentially overcome tumor heterogeneity and drug resistance mechanisms by preferentially accumulating in tumor tissue and binding to cancer cells through the combination of passive and active targeting techniques.

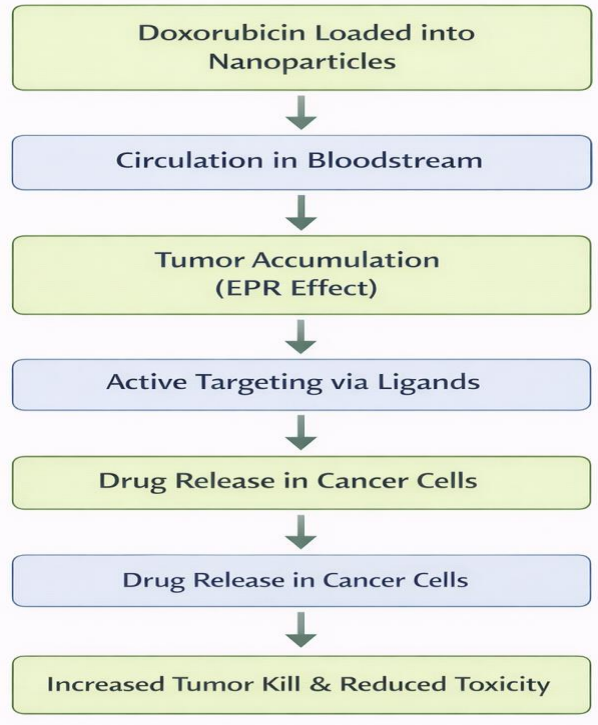


**Figure 1: Flowchart of Doxorubicin Delivery via Nanoparticles**

## 3. CHARACTERIZATION OF DOXORUBICIN-LOADED NANOPARTICLES

Doxorubicin-loaded nanoparticles need to be thoroughly physicochemically characterized in order to guarantee optimal performance and forecast in vivo behavior. This procedure

assesses their size, shape, surface charge, drug loading effectiveness, and release kinetics—all of which have an impact on stability, safety, and therapeutic efficacy.

### 3.1 Size and Morphology

The pharmacokinetics, biodistribution, and cellular absorption of nanoparticles are significantly influenced by their size and shape.Since they can extravasate through leaky tumor vasculature without being quickly cleared by the reticuloendothelial system, nanoparticles in the 10–200 nm range are typically thought to be ideal for tumor targeting via the enhanced permeability and retention (EPR) effect (Blanco et al., 2024). The hydrodynamic diameter and size distribution, which provide information on average particle size and polydispersity, are frequently determined using dynamic light scattering (DLS). High-resolution observation of nanoparticle shape, surface characteristics, and internal structure is made possible by complementary techniques including transmission electron microscopy (TEM) and scanning electron microscopy (SEM), which validate uniformity and spherical or other desired morphologies (Khan et al., 2021; Patel et al., 2021). Predicting circulation time, tumor penetration, and absorption efficiency in cancer cells requires precise control over size and morphology.

### 3.2 Zeta Potential

One important measure of a nanoparticle's surface charge that influences its stability in suspension, aggregation behavior, and interactions with biological membranes is its zeta potential. In order to avoid aggregation and preserve long-term colloidal stability, nanoparticles having high absolute zeta potentials—whether positive or negative—tend to repel one another electrostatically (Das et al., 2020). On the other hand, because they decrease nonspecific protein adsorption and immune system clearance, slightly negative or neutral charges are favored for in vivo applications (Singh et al., 2022). PEGylation and ligand conjugation are examples of surface modifications that can alter zeta potential, enhancing stability, circulation time, and tumor cell selective absorption.

### 3.3 Drug Encapsulation Efficiency

The percentage of doxorubicin that is successfully loaded into nanoparticles in relation to the total amount employed during formulation is measured by encapsulation efficiency (EE%). In order to reduce systemic toxicity and achieve the intended therapeutic effect without increasing the supplied dose, high EE is essential (Jain et al., 2021). The most popular technique for accurately measuring drug loading and isolating free drug from encapsulated drug is high-performance liquid chromatography (HPLC). Additionally, loading effectiveness

can be ascertained by detecting the distinctive absorption peaks of doxorubicin in solution using UV-visible spectroscopy (Kumar et al., 2023). Reaching a high EE guarantees that the drug payload is delivered to tumor tissues in an adequate amount and that the release is controlled throughout time.

### 3.4 Drug Release Kinetics

The release profile of doxorubicin from nanoparticles under physiological or tumor-mimicking settings is assessed using in vitro drug release studies. Predicting in vivo performance and creating formulations that preserve therapeutic medication levels while reducing side effects need an understanding of release kinetics (Zhao et al., 2023). By adjusting surface coatings, crosslinking density, polymer composition, and particle size, controlled or sustained release can be accomplished (Chauhan et al., 2022). In order to replicate the tumor microenvironment, studies frequently use buffer solutions at physiological pH (7.4) or acidic pH. The released doxorubicin is then periodically sampled and quantified using HPLC or UV-Vis spectroscopy. In order to maximize therapeutic results while lowering systemic toxicity, the resulting release profiles may show early burst release followed by sustained or stimuli-responsive release.

## 4. THERAPEUTIC EFFICACY OF DOXORUBICIN-LOADED NANOPARTICLES

Thorough in vitro and in vivo evaluations are necessary to examine the therapeutic efficacy of doxorubicin-loaded nanoparticles and ascertain whether formulation improvements result in significant anticancer effects and decreased toxicity. In comparison to traditional doxorubicin, these studies demonstrate the potential of nanocarrier systems to enhance chemotherapy outcomes.

### 4.1 In Vitro Studies

Before moving on to animal or human research, in vitro cytotoxicity studies are essential for determining how well doxorubicin-loaded nanoparticles can kill cancer cells. The cytotoxicity of nanoparticulate formulations is frequently compared to free doxorubicin using standard assays like MTT (which measures mitochondrial activity as a proxy for cell viability), CellTiter Glo (which quantifies ATP levels as an indicator of live cells), and LDH release (which detects loss of membrane integrity) (Jain et al., 2024).

Because of better cellular uptake by endocytosis and higher intracellular drug retention compared to free drug, nanoparticle formulations frequently exhibit greater cytotoxicity in cancer cell lines. For instance, compared to free doxorubicin at equivalent drug concentrations, polymeric micelle-based doxorubicin has been demonstrated to produce

noticeably higher apoptosis rates in breast and liver cancer cell lines, demonstrating the connection between improved performance and sustained intracellular release and targeted delivery (Huang et al., 2023). Furthermore, functionalization with targeting ligands like peptides or folate enhances cytotoxicity and selectivity against cancer cells that overexpress receptors without appreciably raising toxicity in normal cell lines, highlighting the significance of active targeting in in vitro models.

### 4.2 In Vivo Studies

To assess the behavior of doxorubicin-loaded nanoparticles in intricate biological systems, such as pharmacokinetics, biodistribution, tumor inhibition, and systemic toxicity, in vivo animal studies are essential.

- **Pharmacokinetics:** By preventing quick renal clearance and lowering absorption by the mononuclear phagocyte system, nanoparticles frequently provide longer circulation times than free doxorubicin. For example, in rodent and canine models, liposomal doxorubicin formulations have demonstrated much longer half lives and higher area under the concentration time curve (AUC), allowing for more prolonged drug presence in the bloodstream and improved accumulation at tumor sites (Wang et al., 2023).
- **Tumor Inhibition:** Doxorubicin administered via nanocarriers inhibits tumor growth more than similar doses of free medication, according to numerous studies. Nanoparticle formulations considerably decreased tumor volume while preserving more advantageous systemic characteristics in mouse xenograft models of lung and breast cancer. Both regulated medication release within the tumor microenvironment and improved tumor localization through the EPR effect have been linked to enhanced anticancer effects (Singh et al., 2024).
- **Toxicity:** The decrease in systemic toxicity, especially cardiotoxicity, which is a significant drawback of traditional doxorubicin, is a significant benefit of doxorubicin encapsulated in nanoparticles. When compared to free drug controls, animal studies frequently reveal lower levels of cardiac injury indicators, less weight loss, and less histopathological damage in important organs (Li et al., 2023). These results offer preclinical proof that nanoencapsulation can reduce side effects without sacrificing, and frequently increasing, anticancer activity.

### 4.3 Combination Therapy

Synergistic combination therapy are also made possible by doxorubicin delivery systems based on nanoparticles. Chemotherapy can have more potent anticancer effects when combined with other therapeutic techniques including radiation, immunotherapy, or gene therapy.

In glioblastoma models, for instance, studies examining nanoparticles co-loaded with doxorubicin and radiosensitizers have demonstrated markedly increased tumor cell kill when combined with radiation therapy. This is attributed to both improved drug penetration and enhanced sensitivity to radiation-induced DNA damage (Kumar et al., 2024). Similar to this, incorporating immunomodulatory drugs like immune checkpoint inhibitors into nanoparticle platforms has shown enhanced antitumor immune responses in melanoma models, suggesting that nanoparticles can serve as multipurpose carriers that enable both immune stimulation and direct cytotoxicity (41).

These combined approaches demonstrate the adaptability of nanoparticle systems and offer avenues for future treatment plans that take use of several anticancer mechanisms at once.

## 5. CHALLENGES AND FUTURE PERSPECTIVES

Despite the promising potential of nanoparticle-based doxorubicin delivery systems, several challenges remain:

### 1. Scalability and Manufacturing

- It is still very difficult to produce nanoparticles on a large scale while keeping their size, drug loading, and release characteristics constant.
- Batch-to-batch repeatability is challenging because little changes in temperature, mixing, or solvent removal during fabrication can have a substantial impact on quality (Hussain et al., 2022).
- Clinical translation requires the development of standardized and scalable production methods.

### 3. Toxicity

- o Regardless of the drug cargo, nanoparticles can cause inflammation, oxidative stress, or immunological reactions, particularly in non-target tissues (Sharma & Jain, 2021).
- To assure safety, a thorough preclinical investigation is required, including long-term biodistribution and immunotoxicity tests.
- Toxicity risks can be reduced with the use of biocompatible materials and surface changes.

**4. Regulatory Approval**

- o Because conventional regulations are made for small molecules and basic biologics, nanoparticle-based medications confront difficult regulatory obstacles.
- Clinical development may be delayed by regulatory bodies' need for comprehensive data on pharmacokinetics, toxicity, manufacturing methods, and characterisation (Zhang *et al.*, 2023).
- For quicker clinical translation, more precise guidelines and uniform criteria are required.

**5. Personalized Medicine**

- Tumor heterogeneity limits the effectiveness of "one-size-fits-all" nanoparticle therapies.
- To improve efficacy and minimize off-target effects, customized nanoparticle platforms can be created based on unique tumor profiles, including receptor expression and microenvironment features (Gonzalez et al., 2024).
- Integration with genomic and proteomic profiling can facilitate tailored therapy.

**6. Future Directions and Innovations**

- Site-specific delivery can be improved by creating stimuli-responsive nanoparticles that release medications in response to pH, enzymes, temperature, or light (Li & Sun, 2022).
- Real-time monitoring and adaptive treatment plans are made possible by multifunctional systems that integrate therapy with diagnostic imaging, or "theranostics."
- To overcome present constraints and enhance therapy outcomes, interdisciplinary efforts integrating engineering, biology, and clinical research are crucial.

## 6. CONCLUSION

With many benefits over conventional chemotherapy, nanoparticle-based doxorubicin delivery systems are a major breakthrough in cancer treatment. These technologies improve doxorubicin's pharmacokinetics and lower its systemic toxicity by offering regulated release, increased solubility, and extended circulation duration. These delivery systems raise the therapeutic index of doxorubicin by utilizing the special characteristics of nanoparticles, such as their capacity to actively target cancer cells through surface functionalization and passively accumulate at tumor sites through the enhanced permeability and retention (EPR) effect. Drug delivery can be optimized in a variety of ways by including several kinds of

nanoparticles, including liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, micelles, and dendrimers. Additionally, these technologies make it possible to target tumors more precisely, which lessens the negative side effects of freedoxorubicin, especially myelosuppression and cardiotoxicity. Even while the design and development of these nanoparticles have advanced significantly, there are still obstacles to overcome, especially when it comes to increasing production, guaranteeing consistency, and getting regulatory permission for clinical uses. Additionally, these formulations' safety profiles and possible long-term impacts must be carefully assessed. Future studies should concentrate on enhancing the stability, multifunctionality, and targeting capabilities of systems based on nanoparticles. Furthermore, there is potential to improve treatment results and overcome multidrug resistance (MDR) by combining these systems with additional therapeutic approaches as immunotherapy, gene therapy, and radiation therapy. Customized nanoparticle-based platforms for cancer treatment offer a path toward more potent and less harmful treatments in the future. All things considered, doxorubicin delivery systems based on nanoparticles have enormous potential to enhance the clinical management of cancer and could completely change the way chemotherapy is given, offering more efficient, secure, and focused cancer therapies.

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## 8. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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