Therapeutic Frontiers in Nanozyme-Based Cancer Treatment: Advances, Challenges, and Future Directions

D.M. Silva and A.I. Kuruppu

Institute for Combinatorial Advanced Research and Education, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka.

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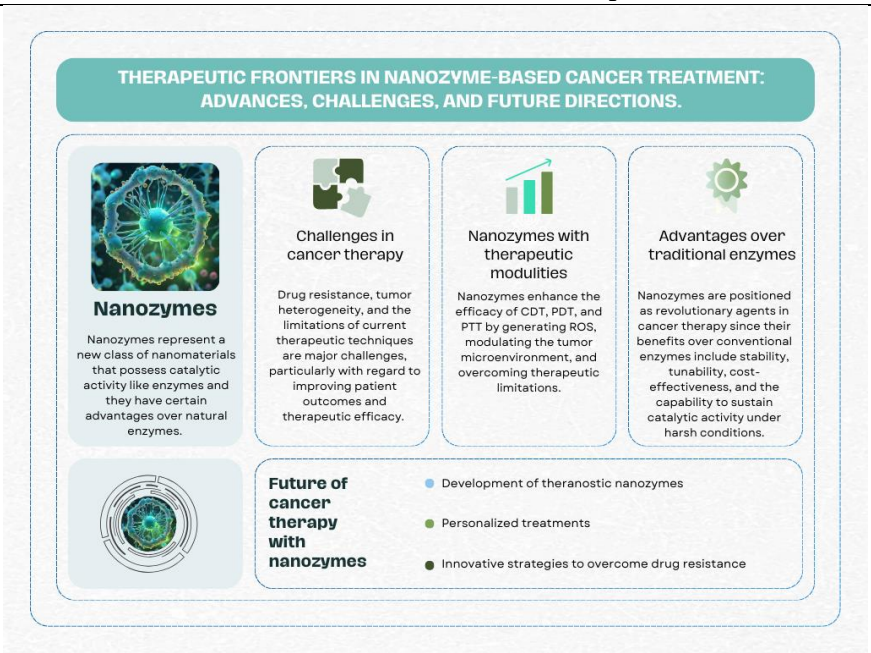

Abstract

Nanozymes, artificial nanomaterials mimicking enzyme activity, are at the forefront of innovative cancer therapies, particularly in chemodynamic therapy (CDT), photodynamic therapy (PDT), and photothermal therapy (PTT). Their capacity to selectively generate reactive oxygen species under tumor-specific conditions, including low pH and high H_2O_2 levels, facilitates targeted induction of cancer cell death while minimizing damage to healthy tissues. When integrated with PDT or PTT, nanozymes enhance oxidative stress and promote immunogenic cell death, further amplifying anti-tumor immune responses. Recent advances in single-atom nanozymes and intelligent nanozymes have shown promise in overcoming therapeutic limitations, such as tumor hypoxia and immune suppression while modulating the tumor microenvironment to boost treatment efficacy. Additionally, ongoing preclinical and clinical evaluations highlight the potential of nanozymes to synergistically enhance immunotherapy outcomes. Their advantages over traditional enzymes, such as stability, tunability, cost-effectiveness, and the ability to maintain catalytic activity in hostile environments, position nanozymes as transformative agents in cancer therapy. However, their clinical translation faces significant challenges, including biocompatibility concerns, delivery inefficiencies to tumor sites, and stringent regulatory hurdles, which require comprehensive research and innovative solutions to address. Despite these limitations, advancements in nanozyme design and functionalization continue to pave the way for more effective and safer applications in cancer therapy which will be discussed in detail in this review.

Keywords: *Cancer therapy, Nanomaterial, Nanozymes, ROS, chemodynamic therapy (CDT), photodynamic therapy (PDT), and photothermal therapy (PTT)*

**Correspondence: kuruppua@kdu.ac.lk*

1. Introduction

1.1. Challenges in Cancer Therapy

Cancer therapy faces significant obstacles, particularly in improving treatment efficacy and patient outcomes. Drug resistance, tumor heterogeneity, and the limitations of current therapeutic techniques are all significant challenges. Drug resistance, a key challenge, can be either intrinsic or acquired, complicating treatment and frequently leading to treatment failure and metastasis in cancer. This resistance stems from intricate signaling networks of cancer cells, which allow them to adapt and dodge therapy, emphasizing the need for innovative medicines that can overcome these barriers (Nagaraju & Kamal, 2019). Another critical barrier is tumor heterogeneity, represented by the genetic and phenotypic features of tumors. This complicates the finding of effective treatment options because many targeted therapies confer clinical benefits only on small subsets of patients. Tumor heterogeneity also challenges precision oncology because the clinical interpretation of genomic data remains difficult, further limiting personalized treatment approaches (Zugazagoitia et al., 2016)**.** Additionally, side effects and limitations of the current chemotherapy and radiotherapy have adverse impacts on the quality of patients' lives. Most of the conventional therapies are burdened by serious side effects and technical and clinical limitations that restrict their efficacy and wider applications (Gyanani et al., 2021). Despite advancements in cancer therapy, these ongoing challenges highlight the need for innovative approaches to improve cancer treatment outcomes.

1.2. Nanotechnology in Cancer Therapy

Nanotechnology plays a transformative position in enhancing cancer treatment by improving drug delivery systems and minimizing side effects. By utilizing nanocarriers, including liposomes, micelles, quantum dots, and polymeric nanoparticles, therapies are capable of achieving targeted delivery to tumor sites, increasing drug efficacy while reducing systemic toxicity (Dessale et al., 2022; Ghazal et al., 2024)**.** The above advancements have led to success rates in drug delivery reaching up to 95% (Karahmet Sher et al., 2024). Nanotechnology enables controlled release, offering a sustained therapeutic effect while reducing the need for high dosages (Dessale et al., 2022; Y. Xu, 2024). Another important advantage is that nanoparticles can be designed for active targeting in drug delivery; they selectively attach to the cancer cells, enhancing the treatment efficacy and minimizing toxicities to normal cells, thereby reducing the usual side effects of chemotherapy (Ghazal et al., 2024; Karahmet Sher et al., 2024). Other important advantages include increased solubility and stability of poorly water-soluble drugs, enriching their therapeutic potential by employing nanotechnology (Ghazal et al., 2024). Multifunctional nanomedicines can combine these benefits, further enhancing treatment outcomes (Dessale et al., 2022). Despite all these developments, there are yet several concerns about the long-term safety, possible toxicity, and biocompatibility of nanomaterials, which require further research to ensure clinical feasibility (Y. Xu, 2024).

Nanozymes stand in for a new class of nanomaterials exhibiting enzyme-mimetic catalytic activity and distinctly enjoy advantages over natural enzymes in many applications, including cancer therapy. They mimic the catalytic functions of natural enzymes with superior structural integrity, lower cost, tunability, and reduced immunogenicity; hence, they could be potential candidates to overcome drawbacks in conventional nanomaterials. Nanozymes can mimic several enzyme-driven reactions, including catalase, superoxide dismutase, peroxidase, and oxidase. Consequently, they demonstrate greater robustness relative to natural enzymes and can be manufactured at lower costs, thus making scaling production easier. In addition, their catalytic efficiency and substrate specificity can easily be altered to allow tailored therapeutic applications (Sen et al., 2024).

*Correspondence: kuruppua@kdu.ac.lk

2. Classification of Nanozymes in Cancer Therapy

There are two main classifications of nanozymes. The first classification groups them based on their catalytic mechanisms, categorizing nanozymes by the type of reactions they facilitate. The second classification focuses on their composition, grouping nanozymes according to the materials they are composed of. Both categories are detailed in Figure 1.

2.1. Catalytic Mechanism-Based Classification

Nanozymes are classified based on the types of natural enzymes they mimic, with each group catalyzing specific reactions crucial for cancer therapy. The most common types of nanozymes include oxidase, peroxidase, superoxide dismutase, and catalase-like mimics, each demonstrating distinct catalytic mechanisms with significant potential or existing applications in cancer therapy.

2.1.1. Oxidase-like Nanozymes

Nanozymes with an oxidase-like activity mimics the generation of reactive oxygen species (ROS), together with the behaviors of oxidases while catalyzing substrate oxidations in the presence of oxygen. These ROS include superoxide anions, which can induce oxidative stress within the tumor microenvironment (TME) and lead to selective tumor cell death. Therefore, oxidase-like nanozymes might be promising candidates for applications in cancer therapy. For example, Cerium Oxide (CeO_2) nanoparticles exert activities such as that of oxidases under the acidic conditions inside tumors, which enhance their therapeutic applications (Y. Huang et al., 2019).

2.1.2. Peroxidase-like nanozymes

Peroxidase-like nanozyme catalyzes the decomposition of Hydrogen Peroxide (H_2O_2) into hydroxyl radicals (•OH), highly active oxidants competent in damaging cell membranes, DNA, and other crucial components of cancer cells. One of the renowned peroxidase mimics has been Iron Oxide nanoparticles (Fe_2O_3), taking advantage of the high H_2O_2 level in tumors. The generated hydroxyl radicals induce oxidative damage to cells and thereby promote the apoptosis of the cancerous cells (Y. Huang et al., 2019).

2.1.3. Superoxide dismutase (SOD)-like nanozymes

SOD-like nanozymes catalyze the harmful superoxide radicals to hydrogen peroxide and oxygen, modulating the oxidative stress in the TME. By regulating ROS levels, these nanozymes protect normal tissues while increasing oxidative damage to tumor cells, especially when combined with other therapies that promote ROS generation (Y. Huang et al., 2019).

2.1.4. Catalase-like nanozymes

Catalase-mimicking nanozymes catalyze H_2O_2 into water and oxygen. Consequently, this activity may serve as a means of increasing oxygen levels in hypoxic tumor areas. This can amplify the effectiveness of oxygen-dependent therapies such as radiotherapy and photodynamic therapy (PDT). Increased oxygen availability in the TME enhances their lethal effects on tumor cells (Y. Huang et al., 2019).

2.2. Material-Based Classifications

Nanozymes can be categorized based on the materials they are made from, each with unique physical and chemical properties that influence their stability, biocompatibility, and efficiency in cancer therapies.

*Correspondence: kuruppua@kdu.ac.lk

2.2.1. Metal Nanozymes

The unique catalytic properties of metal-based nanozymes, such as those made from iron oxide, gold, and silver, have made them important constituents in cancer therapy. Iron oxide nanoparticles (Fe_2O_3) are well noted among metal oxides for their peroxidase-like activity; they catalyze the decomposition of hydrogen peroxide into ROS, leading to oxidative damage in cancer cells. They are also efficient in the assistance of radiotherapy by producing ROS in the TME, therefore sensitizing the tumor cells to radiation therapy. Their magnetic property enables targeted hyperthermia treatment where localized heat can lead to death in tumorous cells (Shestovskaya et al., 2023).

The other major application of gold nanoparticles (AuNP) is in photothermal therapy (PTT), which depends on the optical properties of these nanoparticles, especially their surface plasmon resonance (SPR). AuNPs absorb near-infrared light and then convert it to heat in PTT, leading to the death of cancerous cells while trying as much as possible not to damage healthy tissue lining around the tumor area. Additionally, AuNPs can be altered with different targeting molecules to enhance drug delivery, ensuring higher accumulation in tumor cells and reduced systemic toxicity (P. Singh et al., 2018).

The hybrid nanozyme Fe_2O_3/Au can update the designs of nanozymes based on metals by incorporating the catalytic function of iron oxide with the photothermal one of gold. This hybrid nanozyme carries out a biocatalytic cascade in the TME and therefore provokes a heating effect from photothermal conversion in addition to both oxidative stress and ferroptosis. It is the multi-faceted approach that makes cancer therapy more efficient by attacking tumor cells along several pathways, such as starvation, oxidative stress, and hyperthermia. Thus, it also functions effectively in the treatment of aggressive cancers, including even triple-negative breast cancer (Zeng et al., 2023; X. Zhang et al., 2022).

2.2.2. Carbon Nanozymes

With their unique physicochemical properties, carbon nanozymes have emerged as versatile platforms for cancer therapy, including excellent stability, tunable catalytic activities, and a high surface area. These enzymes, which mimic natural enzymes, have a wide range of applications in the diagnosis and treatment of cancer, especially concerning their peroxidase-like activities. Peroxidase-like activity has been engineered on a few carbon-based nanozymes, catalyzing reactions to produce ROS, which eventually induces cell oxidative stress, leading to the selective killing of the cancerous cells (Wang et al., 2021). More recently, carbon-based nanozymes have been incorporated into multi-functional therapeutic platforms. Studies have pointed out a photoresponsive carbon-based nanozyme that is capable of detecting and depleting intracellular glutathione, believed to be a key antioxidant in cancer cells that promotes resistance against ROS-induced damage. Depletion of glutathione by these nanozymes increases the effectiveness of ROS-based therapies, hence making them powerful tools in cancer treatment (Yi et al., 2024). Research indicates that carbon nanoparticles, due to their nanozyme activity, can induce DNA repair mechanisms in cancer cells, potentially leading to resistance against poly ADP-ribose polymerase inhibitors (Fan et al., 2018). Consequently, carbon nanozymes serve a dual role as therapeutic agents and modulators of DNA repair pathways. This complexity poses challenges in targeted therapies, as they may enhance treatment efficacy while also promoting resistance. Additionally, these nanozymes are used in biosensing for early cancer detection due to their high catalytic efficiencies and ligand functionalization, enabling accurate cancer cell identification. The potential of these carbon-based nanozymes as multifunctional agents for real-time cancer monitoring and treatment is promising (X. Zhang et al., 2022).

*Correspondence: kuruppua@kdu.ac.lk

2.2.3. Organic and Hybrid Nanozymes

Organic and hybrid nanozymes, particularly those developed from metal-organic frameworks (MOFs) and polymers, have been recognized as promising tools in precision oncology. MOF-based nanozymes demonstrate versatile catalytic activities (e.g., oxidase and peroxidase mimicry), which, coupled with their stimuli-responsive properties, enable controlled drug release in response to the TME, maximizing therapeutic effects while minimizing off-target effects (Yan et al., 2024; Ullah Khan et al., 2024). They also promote ROS generation, enhancing oxidative stress in cancer cells to drive cell death (Bu et al., 2024). In parallel, polymer-based nanozymes, known for their biocompatibility and stability, can be functionalized for targeted drug delivery, thereby increasing therapeutic precision with minimal side effects (Y. Zhang et al., 2024; Ullah Khan et al., 2024). Both organic and hybrid enzymes hold significant potential for cancer therapy applications; however, researchers encounter several challenges in translating them into clinical practice. Refining their design for consistent performance and minimizing side effects are some of the key areas under continuous research to ensure the effectiveness and safety of these enzymes in different therapeutic applications.

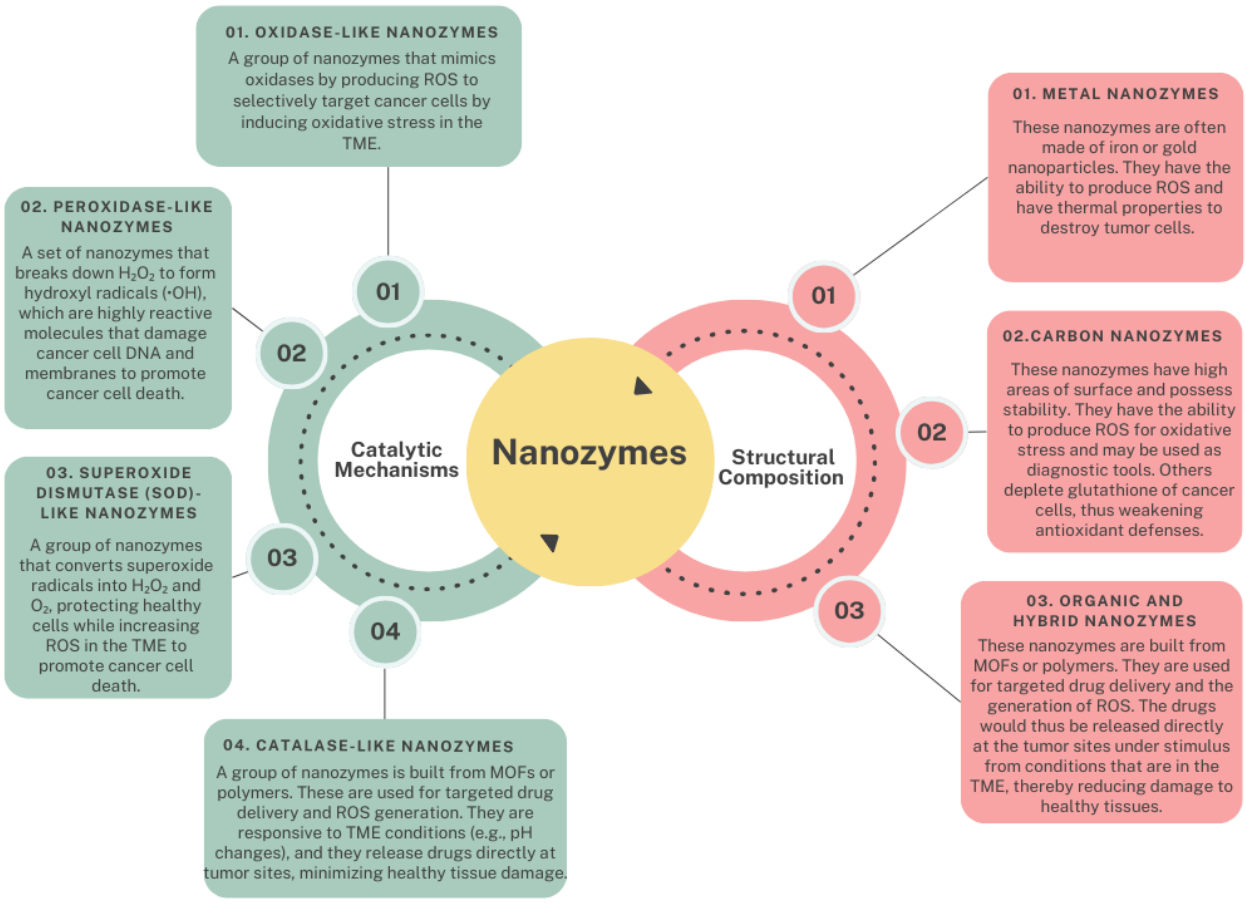

Figure 1: The two main classifications of nanozymes; based on their catalytic mechanisms and their composition

*Correspondence: kuruppua@kdu.ac.lk

3. Mechanisms in Cancer Therapy of Nanozymes

3.1. Reactive Oxygen Species (ROS) Generation

Nanozymes are important in producing ROS, which cause oxidative stress in cancerous cells, thereby killing them. Iron oxide nanoparticles (Fe_2O_3) act as peroxidase-like nanozymes, catalyzing the breakdown of hydrogen peroxide into hydroxyl radicals that trigger apoptosis (Gao et al., 2007). TME contains high levels of H_2O_2, enhancing the efficacy of nanozymes (Fan et al., 2018). Cerium oxide nanoparticles exhibit both oxidase and catalase activities, increasing local ROS in the acidic TME (Celardo et al., 2011). Additionally, catalase-like nanozymes convert H_2O_2 into oxygen, improving oxygen availability in hypoxic tumor areas and enhancing oxygen-dependent therapies such as radiation and photodynamic therapy (PDT) (Celardo et al., 2011). Overall, nanozymes selectively amplify oxidative stress in the TME, making cancer cells more sensitive to therapies (Fan et al., 2018; Celardo et al., 2011).

3.2. Synergistic Effects with Other Therapies

Nanozymes have demonstrated significant potential in enhancing the efficacy of conventional cancer treatments through their synergistic effects. They can enhance oxidative damage to cancer cells when used in conjunction with chemotherapy, making them more vulnerable to chemotherapeutic drugs. For example, when combined with chemotherapy medications, FeO_4 nanoparticles not only generate ROS but also improve the drug absorption and distribution into tumor cells (Soetaert et al., 2020).

4. Nanozymes in Therapeutic Modalities

Nanozymes offer flexibility across multiple cancer therapies, notably chemodynamic therapy (CDT), PDT, and PTT, with added synergy in combination with immunotherapy. Through precise targeting and efficient ROS generation, nanozymes promote tumor cell death while enhancing immune responses, paving the way for improved cancer treatments (Shestovskaya et al., 2023; P. Singh et al., 2018; X. Zhang et al., 2022).

4.1. Chemodynamic Therapy (CDT) and Synergistic Effects with PDT/PTT

Nanozymes, acting as enzyme mimics, are increasingly employed in CDT due to their ability to catalyze ROS production under tumor-specific conditions, such as low pH and high H_2O_2 levels found in the TME. This selective generation of ROS can induce the death of cancer cells while minimizing harm to healthy tissue. When combined with PDT or PTT, nanozymes enhance oxidative stress and promote immunogenic cell death (ICD), which activates anti-tumor immune responses, thus further amplifying therapeutic efficacy (Shestovskaya et al., 2023; P. Singh et al., 2018). Research shows promising results when multifunctional nanoparticles combine CDT with PDT/PTT, particularly in breast cancer therapy. These combined approaches not only lead to localized tumor destruction but also stimulate systemic immune responses, especially when integrated with anti-PD-L1 immunotherapy. This immunotherapy approach blocks inhibitory signals from tumor cells, thereby boosting T-cell-mediated immunity and enhancing overall tumor eradication (Qian et al., 2022; Zeng et al., 2023). Furthermore, nanozymes used in CDT, PDT, and PTT can overcome challenges related to ROS generation, target hypoxic tumor regions effectively, and minimize off-target toxicity, demonstrating that these multifunctional nanomaterials have significant potential for more durable cancer therapies (P. Singh et al., 2018; Zeng et al., 2023).

4.2. Photodynamic Therapy (PDT) and Nanozymes

PDT, non-invasive cancer therapy, uses light-activated photosensitizers to generate ROS, which selectively destroy cancer cells. Nanozymes enhance PDT efficacy by amplifying ROS production and by acting as carriers to improve photosensitizer accumulation within

*Correspondence: kuruppua@kdu.ac.lk

tumors. This increased accumulation ensures that even poorly vascularized tumor regions receive sufficient therapeutic exposure. Additionally, nanozymes address the oxygen-deficient nature of tumor tissues by providing supplementary oxygen, a critical element for ROS generation in PDT, thereby enhancing oxidative stress within cancer cells (Zhao et al., 2024; George & Abrahamse, 2024). The integration of nanozymes with PDT enhances tumor specificity, as nanozyme-based PDT has shown superior tumor suppression while reducing damage to surrounding normal cells. This specificity extends the action of PDT, overcoming the challenge of limited light penetration in deep-seated tumors. The application of nanozymes in PDT continues to be a promising area for research, with the potential to optimize tumor targeting, reduce side effects, and maximize therapeutic outcomes (Ma, 2024; Zhao et al., 2024).

4.3. Photothermal Therapy (PTT) with Nanozymes

PTT, a promising cancer treatment, relies on nanoparticles for energy conversion into localized heat with selective destruction of tumor cells. Recently, nanozymes have been integrated into PTT protocols to enhance treatment specificity and efficiency through their unique catalytic properties. AuNPs can absorb near-infrared light and convert it into heat, to induce apoptosis in cancer cells through hyperthermia (Kim & Kim, 2024b). Their catalytic roles can further enhance such effects and provide a more specific action on cancerous cells while sparing normal tissues surrounding cancer (Chuang et al., 2024). The combination of PTT with nanozymes offers several advantages. Nanozymes are engineered to target specific tumor markers, offering an enhanced specificity that leads to the improvement in the precision of treatments and reduces off-target effects (Ye et al., 2024). PTT has been clinically evidenced to elicit synergistic effects with immunotherapy and thus enhance treatment efficacy by eliminating not just cancer cells but also by potentially provoking anti-cancer immune responses (Kim & Kim, 2024a). Recent breakthroughs in PTT are represented by new nanoparticle designs, such as encapsulation with red blood cell membranes, which allow for longer circulation time and enhanced tumor accumulation, thus more effective localization of heat (Ye et al., 2024). Optimization of important parameters in PTT-nanoparticle size and laser intensity has also led to better treatment outcomes. However, deeper tissue penetration and methods to avoid nanoparticle immune-mediated clearance remain important obstacles to be addressed (Kim & Kim, 2024a). Overcoming these challenges will be important in the maximizing clinical outcomes of PTT in cancer therapy (Dong et al., 2024).

5. Advantages of Nanozymes Over Traditional Enzymes

Nanozymes are artificial nanomaterials that mimic natural enzymes, demonstrating enzyme-like activities including oxidase, peroxidase, superoxide dismutase, and catalase functions (S. Li et al., 2024). By modifying their size, surface chemistry, and composition, nanozymes achieve targeted catalytic functions, making them versatile for oncology applications (D. Zhang et al., 2024). Unlike traditional enzymes which are natural proteins sensitive to temperature and pH, nanozymes offer enhanced stability, lower production costs, and effective functionality in complex biological environments (Cuoghi et al., 2024; W.-L. Li & Head-Gordon, 2021). Their ability to maintain catalytic activity in hostile conditions, such as the TME, underscores their innovative potential in cancer treatment (Bu et al., 2024; X. Xu et al., 2024).

5.1. Stability and Robustness

Compared to natural enzymes, nanozymes have far greater stability, withstanding the high pH and temperature conditions typically encountered in therapeutic settings. This extended stability enhances their catalytic activity across diverse environments, making them more

*Correspondence: kuruppua@kdu.ac.lk

suitable for biomedical applications (Yadav & Singh, 2021). For example, single-atom metallic enzymes and metallic nanozymes exhibit superior thermal and solvent tolerance compared to natural enzymes (Dhanjai et al., 2020; Bhagat et al., 2021; D. Zhang et al., 2024).

5.2. Tunability and Customization

Nanozymes' adaptable catalytic properties make them highly versatile for various therapeutic applications. This flexibility arises from adjusting the chemical composition, particle size, and surface modifications in biomedical contexts.

5.2.1. The particle size

To increase the catalytic efficacy of nanozymes, the size and chemical makeup of particles have proven crucial. For example, through tuning support materials and adjusting nanoscale sizes, single-atom nanozymes can achieve effectiveness in targeted therapies. Nanozyme engineering at the nanoscale (1 to 100 nm) enhances catalytic efficiency, surpassing conventional enzymes in biological reactivity and precise targeting across various applications (Chan et al., 2023). Besides, such tailoring in 2D nano biocatalysts through synthesis-structure relationships, active site design, and surface modification increases their performances for biomedical applications drastically (Cui et al., 2024).

5.2.2. Surface Modification

Surface modifications enhance the functionality of nanozymes through enhanced target binding affinity. The modification of the surface further assists biochemical recognition, regulates surface charge, and influences catalytic performance; all factors important towards specific therapeutic targeting (Hou & Xianyu, 2023).

5.2.3. Chemical Composition

Chemical composition is another important modulator for the optimization of nanozyme activity. For example, single-atom incorporation results in a great increase in catalytic rates, which shows that composition is an effective approach for designing highly active nanozymes (Chan et al., 2023). More importantly, active components can be encapsulated into MOFs through confinement effects to further enhance the stability and catalytic activity of nanozymes (Zhu et al., 2022). While the advantages of customization are realized, it is also a fact that the persistent challenge to achieve consistent performance across different applications suggests the need for further research in the design and synthesis of nanozymes.

5.3. Cost-Effectiveness

Nanozymes are more cost-effective than natural enzymes, thus making them a more viable option for wide-scale applications in cancer treatment.

5.3.1. Production Cost

Compared to natural enzymes, nanozymes are simpler to make, particularly when discussing carbon nanomaterials, because they do not require the intricate extraction and purification procedures that biological enzymes typically require. Nanozymes could therefore be a viable choice for wider cancer treatment applications, guaranteeing therapeutic accessibility on a bigger scale (Gomaa, 2022; Han & Yoon, 2020; Sun et al., 2018; Yang et al., 2024).

5.3.2. Catalytic Activity

The reputation of nanoenzymes as a low-cost substitute for natural enzymes is further reinforced by their strong catalytic activity and minimal preparation costs. Due to prolonged

*Correspondence: kuruppua@kdu.ac.lk

catalytic efficiency being essential for therapeutic efficacy in cancer therapy, their enzymatic mimicry is perfect for the above applications (Gomaa, 2022; Yang et al., 2024).

5.3.3. Stability and Scalability

Nanozymes could be produced on an industrial scale, stored for a long time, and show exceptional stability in challenging environments. This supports the systems' economic efficiency in a clinical context and benefits from the practicality that this provides for medical applications by lowering the costs related to storage and/or degradation of the systems (Sun et al., 2018; Yang et al., 2024).

5.3.4. Theranostic Strategies

The stability of nanozymes and their catalytically active functioning at the TME provides a tailored treatment, which in turn leads to cost-effectiveness and better patient outcomes in theranostic techniques that combine therapeutic and diagnostic activities. These characteristics make the nanozymes advantageous over the conventional enzymes in the treatment of cancer (Gomaa, 2022; Sun et al., 2018).

6. Challenges and Limitations in Cancer Therapies Using Nanozymes

The applications of nanozymes in oncological treatment are facing several major obstacles and limitations despite their promise.

6.1. Biocompatibility and Toxicity

A major disadvantage of using nanozymes for cancer treatment could be their biocompatibility. The majority of nanozymes, with their heavy metals or toxic components, can exhibit cytotoxicity that could overshadow therapeutic benefits. Carbon nanotubes and nanozymes made of metals have generated concerns because of the cytotoxic nature of such materials (Tian et al., 2023; X. Xu et al., 2024). Research shows that though certain nanozymes have proved to induce apoptosis in malignant cells, their effect on healthy cells is a major concern and has to be considered. A balance between therapeutic efficiency and safety is necessary; therefore, biocompatibility tests must be carried out thoroughly to establish safe dosage thresholds and minimize adverse effects. Furthermore, studies have demonstrated that nanozymes might trigger immunological reactions that result in tissue damage and inflammation, thereby exacerbating therapy effects. There are issues about the long-term biocompatibility of nanozymes and their possible harmful effects on healthy tissues, particularly if they aggregate in organs that are not their intended target (Cai et al., 2023). Additionally, the importance of utilizing the TME for effective treatment has been underlined, although this ignores the challenges of efficiently delivering nanozymes to tumor sites (X. Xu et al., 2024). Moreover, challenges associated with nanozyme technology stem from its interaction with biological fluids. One of the major issues is that when nanoparticles come into contact with biological fluids, they are rapidly coated with a protein-based corona, which alters their subsequent interactions with cells and tissues. Unexpected side effects or toxicity in non-targeted organs may result from such bio-corona's alteration of distribution, targeting effectiveness, and immune response. The long-term buildup of these nanozymes, particularly those accumulating outside of tumor tissues, may increase certain toxicity risks that require more research (Rosini et al., 2023).

6.2. Delivery Efficiency

A major challenge in employing nanozymes for cancer treatment is their effective delivery to tumor locations. Two common factors that will improve the treatment result of nanozymes are their deep penetration into solid tumors and their slow immune system clearance.

*Correspondence: kuruppua@kdu.ac.lk

Numerous studies have demonstrated that the physicochemical characteristics of nanozymes are important determinants of their bio-distribution and targeting (Rosini et al., 2023; Sindhu et al., 2021). For instance, mesoporous nanozymes are designed to improve the generation of ROS in the TME specifically. However, this also requires overcoming the obstacle of effectively delivering agents to tumor sites with stability in circulation (X. Zhang et al., 2022).
Carbon nanotubes can also be functionalized with specific agents that enhance targeting efficiency; however, overall effectiveness in terms of tumor penetration is still very low. This can dramatically alter the targeting capacity and bio-distribution of nanozymes. Delivery through this channel is made more difficult by the fact that the protein-based corona's thickness and composition vary based on the properties of the nanoparticles and the biological environment (Rosini et al., 2023)**.** For this reason, current research focuses on optimizing nanozyme and delivery system designs to enhance accumulation at tumor sites, thereby improving therapeutic outcomes.

6.3. Regulatory Hurdles

Several regulatory challenges hinder the full-scale clinical application of nanozymes in cancer therapy. Significant safety and effectiveness data are needed for clinical approval, together with a thorough assessment of nanozyme characteristics for pharmacokinetics and biodistribution to guarantee that regulatory requirements are fulfilled (Sindhu et al., 2021). Additionally, the development of standardized production and characterization procedures is necessary for the translation of nanozyme technology from laboratory to clinical settings (X. Zhang et al., 2022).

Innovative nanozyme systems confront significant challenges in obtaining regulatory approval, despite their bright future. Before being used in a clinical setting, extensive safety assessments and therapeutic efficacy validation must be completed (Tang et al., 2022). Moreover, the regulatory pathway to the approval of new nanozyme formulations is particularly cumbersome, considering all the details regarding long-term safety and effects on human subjects which is a reason for thorough reviews (Tan et al., 2022)**.** While the above issues are being resolved, detailed documentation concerning the safety, efficacy, and consistency of the production of nanozymes is still an essential need concerning overcoming some potential regulatory barriers (Rosini et al., 2023; X. Xu et al., 2024).

7. Recent Trends and Advances in Nanozyme Research

7.1. Nanozymes with Multifunctionality

The adaptability of multi-functional nanozymes has significantly transformed cancer treatment methodologies. Atomically dispersed metal-centered nanozymes (Single-Atom Nanozymes) have demonstrated especially notable potential owing to their remarkable atomic efficiency and distinctive catalytic characteristics (Tian et al., 2023; X. Xu et al., 2024)**.** Comprising single-atom catalysts such as platinum and cerium, single-atom nanozymes facilitate the accurate regulation of ROS concentrations within the TME. This culminates in a proficient CDT by enhancing oxidative stress, which subsequently induces apoptosis in cancer cells (Cai et al., 2023; Tian et al., 2023).

Particularly, one condition that makes these nanozymes very promising is the function of overcoming common therapeutic limitations; for instance, tumor hypoxia significantly decreases the effectiveness of therapies such as radiotherapy. For example, platinum-based single-atom nanozymes have shown the capability to enhance the efficiency of radiotherapy through oxygen production in hypoxic regions within tumors (Ren et al., 2022; X. Xu et al., 2024)**.**

*Correspondence: kuruppua@kdu.ac.lk

7.2. Intelligent Nanozymes

Smart nanozymes represent the cutting edge in the development of cancer therapy owing to their capability for precise manipulation of therapeutic actions. These nanozymes are engineered to respond to specific conditions that prevail within the TME, such as acidic pH or low oxygen levels. Hypoxic environments activate platinum and iron-based nanozymes, which then go ahead to produce ROS, thereby acting synergistically and enhancing the efficacy of chemotherapy and radiotherapy, respectively (Ren et al., 2022).

Besides, nanozymes modulating immune responses are emerging as well as critical players in cancer immunotherapy. Nanozymes strategically designed to modulate tumor metabolism have the potential to induce immunogenic cell death and simultaneously reprogram tumor-associated macrophages from a tumor-supportive M2 phenotype toward a tumor-restraining M1 phenotype. Such reprogramming enhances not only the immune system's capability of targeting cancer cells but also elevates the efficacy of checkpoint blockade therapies (C. Huang et al., 2022; Ramesh et al., 2022).

7.3. Preclinical and Clinical Studies

Numerous therapies utilizing nanozymes are presently in various stages of preclinical and clinical evaluation, yielding encouraging outcomes. Specifically, single-atom nanozymes are being researched for their capacity to selectively target cancerous cells while preserving adjacent healthy tissue, attributable to their elevated specificity and adjustable catalytic functionality (Tian et al., 2023)**.** Investigations conducted in preclinical settings have demonstrated that nanozymes can significantly bolster the immune system's response to tumors, positioning them as promising candidates for synergistic applications alongside immunotherapies such as checkpoint inhibitors (X. Xu et al., 2024). Multi-functional and intelligent nanozymes open a new era in precision medicine for cancer treatment. However, there is limited evidence of clinical trials specifically investigating nanozymes for cancer treatment. The challenges related to biocompatibility, delivery efficiency, and regulatory approval have slowed their transition into clinical testing. Nevertheless, the strategic use of nanozymes in cancer detection and synergistic cancer treatments could revolutionize oncology treatment in the future.

8. Future Perspectives

When it comes to the treatment of cancer, nanozymes may give rise to several advances. Increasing tumor targeting through surface modification and dual-ligand systems will achieve the specificity of nanozymes with minimal off-target effects to ensure the accuracy of therapy. As the combination therapies get developed further, nanozymes will be at the core of enhancing effectiveness against immune checkpoint inhibitors through intensifying immune responses and overcoming challenges presented by immune suppression in the TME. In addition, nanozymes designed according to a patient's tumor will revolutionize personalized medicine with very precise treatments and fewer side effects. Another important approach will be overcoming drug resistance by the modulation of the TME through nanozymes, the inhibition of resistance mechanisms, and the improvement in treating advanced cancers. The development of theranostic nanozymes, which merge therapy and diagnostics, will allow real-time monitoring and dynamic treatment adjustments, enhancing both efficiency and efficacy. Biodegradable nanozymes will eliminate safety concerns by degrading after treatment, hence reducing toxicity in the long term. Innovations allowing nanozyme to better penetrate complex biological barriers, the dense extracellular matrix typical of many solid tumors will significantly improve drug delivery. As a result, nanozymes may greatly impact the next generation of cancer therapy.

*Correspondence: kuruppua@kdu.ac.lk

9. Conclusions

Nanozymes have emerged as transformative agents in the landscape of cancer therapy by combining stability, specificity, and cost-effectiveness in overcoming some of the major challenges implicated in cancer treatment. Capable of selectively targeting cancerous cells, modulating the TME, and further activating improved immune responses, nanozymes are brilliant candidates to be integrated into various therapeutic modalities. From catalyzing ROS production to inducing immunogenic cell death and reprogramming tumor-associated macrophages, nanozymes have brought about an intelligent, multifunctional approach to oncology. Nanozyme-based treatments, therefore, hold bright prospects for meeting unmet clinical needs and furthering current cancer treatment. As research advances, the development of smarter nanozymes with increased selectivity and multi-modal capabilities could unlock new avenues for truly personalized and highly effective treatment for cancer. This progress may also open new avenues in precision medicine, whereby nanozymes stand at the threshold of improving the therapeutic outcome and reshaping the future of cancer care.

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*Correspondence: kuruppua@kdu.ac.lk