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# Targeted Drug Delivery Using Nanozymes for Improved Rheumatoid Arthritis Outcomes

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## ABSTRACT

Nanozymes, enzyme-like nanomaterials, offer a novel therapeutic approach for rheumatoid arthritis (RA), characterized by severe joint inflammation and cartilage destruction. Traditional RA treatments, such as NSAIDs, immunosuppressants, and biologics, often cause significant side effects and do not directly address the underlying causes of the disease. Nanozymes offer unique properties, including high stability, tunable catalytic activity, and biocompatibility, making them promising candidates for RA therapy. Recent advancements show the efficacy of nanozyme-functionalized exosomes, hydrogels, and encapsulated drugs in targeting inflamed joints, reducing oxidative stress, and promoting cartilage regeneration. Specifically, ultra-small Prussian blue nanoparticle exosomes (uPB-Exo) have shown superior anti-inflammatory effects and targeted delivery capabilities, significantly improving joint health in RA models. These innovative nanozyme-based treatments represent a significant step forward in RA management, promising enhanced therapeutic efficacy with reduced side effects. Further research and clinical trials are essential to validate these findings and optimize nanozyme applications in autoimmune disease therapy.

## Introduction

Autoimmune diseases are a leading cause of death among middle-aged women in the United States (Cooper & Stroehla, 2003). Additionally, 10% of the global population is currently affected by autoimmune diseases, suggesting an urgent demand to treat and ultimately cure these diseases (Li et al., 2023). Due to their chronic and aggressive nature, they can significantly impact the quality of life, specifically, activities of daily living (ADLs). Autoimmune diseases are often chronic diseases, either systematic or organ specific, and are characterized by inflammatory responses to self-antigens (Sudres et al., 2018). They arise from dysregulation in the immune system, where immune cells mistakenly recognize healthy tissues as foreign, triggering inflammation and tissue damage (Wang et al., 2015). Despite decades of research, the causes of autoimmune diseases remain largely unknown and are attributed to factors such as genetics, environment, and lifestyle (Sudres et al., 2018). Rheumatoid Arthritis (RA) is a chronic autoimmune disease that is characterized by severe synovial inflammation and cartilage destruction (Firestein, 2003). These symptoms lead to pain, stiffness, and progressive joint damage; significantly impacting the quality of life and productivity of millions of people worldwide (Firestein, 2003).

Currently, the treatment options available for RA are typically designed to target and suppress the symptoms rather than the disease itself. Despite the extensive array of therapies available, including non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants like disease-modifying antirheumatic drugs (DMARDs) and corticosteroids, their utility is often tempered by significant side effects (Elkhalifa et al., 2018). NSAIDs inhibit cyclooxygenases (COX) enzymes, reducing prostaglandin synthesis and thereby alleviating pain, fever, and inflammation (Bindu et al., 2020). They are effective in managing symptoms of autoimmune diseases such as rheumatoid arthritis, lupus, and ankylosing spondylitis. Adverse effects include gastrointestinal complications, cardiovascular events, liver toxicity, allergic reactions, and impacts on platelet function (Bindu et al., 2020). Immunosuppressants, such as DMARDs and corticosteroids, work by inhibiting immune system activity, thereby suppressing the production of

inflammatory mediators, while also being effective in controlling disease activity and preventing progression (Elkhalifa et al., 2018). However, they increase susceptibility to bacterial, viral, and fungal infections (Elkhalifa et al., 2018). Corticosteroids mimic cortisol to inhibit pro-inflammatory cytokines and suppress immune cell activity. They effectively reduce inflammation but can cause adverse effects like osteoporosis, glucose intolerance, insulin resistance, and increased infection risk with prolonged or high-dose use (Elkhalifa et al., 2018).

To avoid the adverse effects of these therapies, research has been focused on looking for a method to harness the benefits of the traditional therapies while mitigating the side effects. One promising avenue is nanotechnology, an emerging field of science that involves the manipulation of materials and structures at the nanoscale, typically ranging from 1 to 100 nanometers. At this scale, materials often exhibit unique properties and behaviors that differ from their macroscale counterparts, making them ideal candidates for various applications in medicine, including drug delivery and diagnostics (Mekuye & Abera, 2023). Currently, nanomedicine is the leading application of nanotechnology, with drug-development systems utilizing nanoparticles as a method for delivery (Sahu et al., 2021). The integration of nanotechnology into drug development has led to the emergence of nanotechnology-based drugs, which hold great potential for addressing the challenges associated with conventional autoimmune disease treatments. For example, Daunorubicin and Cytarabine Encapsulated in Liposomes (Vyxeos, CPX-351), is a combination chemotherapy nanoparticle that received FDA approval for the treatment of acute myeloid leukemia in August of 2017 (Anselmo & Mitragotri, 2019). Nanotechnology is a promising area in the medicinal field and the health care system due to its unique functional characteristics and features to coordinate with our body's natural system (Sahu et al., 2021).

Nanozymes are a subset of nanoparticles that share their same properties, yet they also exhibit enzyme-like capabilities, such as peroxidase (POD), superoxide dismutase (SOD), and catalase (CAT) activity, which increases stability, bioavailability, and provides additional direct therapeutic benefits (Jiang et al., 2023). They possess the inherent enzymatic abilities which combine the properties of typical chemical catalysts and biocatalysts, making them more desirable than natural enzymes. (Huang et al., 2019). While nanozyme-based drugs are still a novel innovation, a variety of them have been synthesized and tested in recent years. This review will analyze various nanozymes developed used to treat RA and compare it to the efficacy and detriments that traditional treatments entail.

## The Mechanisms of Autoimmune Diseases

The immune system comprises a complex network of cells, tissues, and organs that work together to protect the body from pathogens and maintain physiological balance. It consists of two main branches: the innate immune system, providing rapid, nonspecific responses, and the adaptive immune system, offering specific, long-lasting immunity through the production of antibodies and memory cells (Delves Peter J. & Roitt Ivan M., 2000). Rheumatoid arthritis (RA) is characterized by the immune system attacking its own tissues, leading to severe joint inflammation, pain, stiffness, and swelling (Shah, 2023). RA often strikes small joints in the wrists, hands and feet but can also affect larger joints and other organs such as the eyes and lungs. About 75% of RA patients are women. Symptoms usually start between ages 30 and 50 but can affect people at any age (Shah, 2023).

RA is initiated by lymphocytes that localize to synovial tissue, releasing inflammatory cytokines, recruiting additional immune cells, and increasing synovial fluid production (Smith & Haynes, 2002). T cells enter the synovial tissue and interact with resident macrophage-like type-A synoviocytes that may present unidentified antigens on their surface (Smith & Haynes, 2002). As a consequence of this interaction, the T cells are activated and various proinflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1β), and matrix metalloproteinases (MMPs) are produced. This further perpetuates inflammation and leads to cartilage and bone destruction in the affected joints through osteoclast activation (Figure 1) (Weyand & Goronzy, 2021).

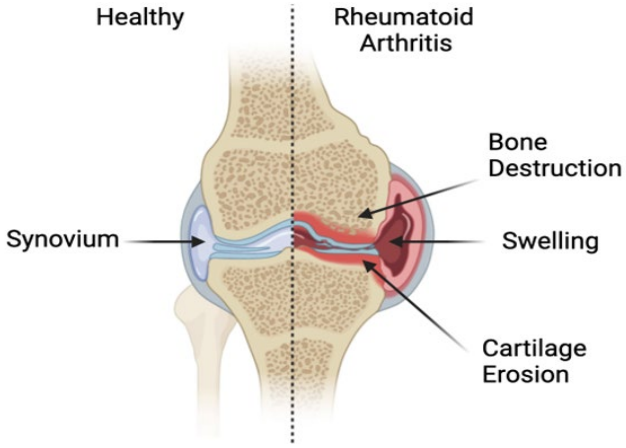


**Figure 1.** Pathophysiology of Rheumatoid Arthritis, characterized by persistent inflammation of the synovial joints, leading to bone destruction, joint swelling, and cartilage erosion.

Osteoclast activation leads to increased metabolic activity and oxygen consumption, leading to the overproduction and excretion of reactive oxygen species (ROS) (Jia et al., 2023). The increased oxidative stress and ROS activity in the inflamed joints suppress the expression and activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) (Jia et al., 2023). SOD normally converts superoxide anions into hydrogen peroxide ($H_2O_2$), while CAT breaks down $H_2O_2$ into water and oxygen (Jia et al., 2023). With reduced SOD and CAT activity, the levels of the superoxide anion ($O_2$–), one of the key ROS produced, and $H_2O_2$ accumulate in the joint tissue (Jia et al., 2023). These reactive oxygen species can directly damage cartilage, bone, and other joint components through oxidative stress mechanisms, exacerbating joint tissue damage in RA (Jia et al., 2023).

## Properties and Applications of Nanozymes

Nanozymes are a class of nanomaterials that exhibit enzyme-like catalytic activities; specifically, they possess characteristics of both enzymes and nanomaterials, combining the efficient catalysis of enzymes with the advantageous properties of nanomaterials. Firstly, they possess catalytic activity similar to natural enzymes, enabling them to catalyze chemical reactions efficiently and specifically (Yang et al., 2021). Additionally, the catalytic performance of nanozymes is highly tunable, allowing for precise control over their activity by modifying factors such as size, morphology, surface chemistry, and composition. This tunability enables customization of nanozymes for specific applications, enhancing their versatility and utility (Yang et al., 2021). Moreover, nanozymes demonstrate remarkable stability, often surpassing that of natural enzymes, and retaining their catalytic activity under diverse environmental conditions, including variations in temperature, pH, and exposure to harsh chemicals. This inherent stability contributes to their durability and longevity in practical applications (Yang et al., 2021). Furthermore, nanozymes exhibit a broad catalytic repertoire, capable of catalyzing a diverse range of reactions such as oxidation, reduction, and hydrolysis (Table 1).

This versatility makes nanozymes advantageous tools across various fields, including drug development and delivery. Nanozymes can be precisely engineered to regulate their substrate selectivity, which in turn improves their catalytic activity, and progresses their multienzyme mimetic activity (Liang & Yan, 2019). They can also serve as effective carriers for drugs or therapeutic agents, encapsulating them and shielding them from degradation. This encapsulation not only protects the drugs but also enhances their bioavailability by facilitating their absorption and distribution throughout the body. By delivering drugs directly to the target site through methods like enzyme-mediated drug activation, nanozymes can mitigate off-target effects and minimize systemic toxicity commonly associated with traditional drug delivery methods (Liang & Yan, 2019). This targeted delivery approach reduces the likelihood of

adverse side effects, enhancing the safety and efficacy of therapeutic interventions. The integration of nanozymes in drug delivery promises to revolutionize medical treatment by offering enhanced precision, improved drug availability, and reduced side effects, thus improving RA patient outcomes (Liang & Yan, 2019).

**Table 1.** Comparison of the Properties of Nanozymes and Natural Enzymes

| **Nanozymes** | **Natural Enzymes** |
|---|---|
| Multienzyme mimetic activity | Single enzyme activity |
| High stability | Limited stability |
| Recyclable utilization | Time-consuming separation and purification |
| Easy to mass produce | Tard to mass produce |
| Cost efficient | High cost |
| Capable of long-term storage | Hard to store long term |
| Robustness to harsh environments | Difficult to utilize in harsh environments |
| Easy to be multi-functionalized | Limited functionalization options |
| Controllable catalytic activity via external stimuli | Uncontrollable catalytic activity and types |
| Unique physicochemical properties | Lack of unique physicochemical properties |

Comparison of the key properties of nanozymes and natural enzymes, showing how nanozymes offer several advantages and unique capabilities over natural enzymes, including multienzyme mimetic activity, high stability, recyclable utilization, ease of mass production, cost efficiency, capability for long-term storage, robustness to harsh environments, easy multi-functionalization, and controllable catalytic activity via external stimuli. Additionally, nanozymes possess unique physicochemical properties lacking in natural enzymes. In contrast, natural enzymes typically exhibit single enzyme activity, limited stability, difficulty in separation/purification and mass production, high cost, challenges in long-term storage and utilization in harsh environments, and limited functionalization options with uncontrollable catalytic activity (Liang & Yan, 2019).

## Nanozymes as Drug Delivery Vehicles

Nanozymes are a broad category that can be divided into smaller subgroups with unique qualities. Exosomes, a type of nanozyme, combine the advantages of synthetic and cell-mediated carriers, presenting significant potential in drug delivery. They evade rapid immune clearance, reduce biotoxicity associated with synthetic vehicles, and simplify the complexities inherent in cell-mediated systems, positioning them as promising next-generation drug delivery vehicles (Zhang et al., 2022). A notable development in this field is the creation of nanozyme-functionalized neutrophil-derived exosomes, specifically designed to diminish the inflammatory environment in RA-affected joints. In this study, neutrophils were harvested from mouse bone marrow and integrated with ultra-small Prussian blue nanoparticles (uPB) to form uPB-Exo (Figure 2). These uPB-Exo nanozymes selectively accumulate in activated fibroblast-like synoviocytes, and while the reason behind the selective accumulation was not stated, it led to the neutralizing of pro-inflammatory factors and thereby alleviating inflammation (Zhang et al., 2022). They also target inflamed joints *in vivo*, clearly identified in MRI-imaging, and effectively inhibit proinflammatory factors. This relieves inflammation and

prevents cartilage damage by regulating Th17 cell balance in murine macrophages, specifically RAW 264.7 cells (Zhang et al., 2022). In cartilage-induced arthritis (CIA) mice with advanced-stage RA, uPB-Exo demonstrated superior efficacy in reducing paw swelling and ankle diameters compared to free uPB and anti-TNF-α treatments. Histological analysis further revealed that uPB-Exo could alleviate synovial inflammation and decrease cartilage destruction, indicating its therapeutic potential in RA management (Zhang et al., 2022). Moreover, uPB-Exo significantly reduced the expression of proinflammatory cytokines TNF-α, IL-1β, and IL-6, both locally in joint tissues and systemically in serum, highlighting its potent anti-inflammatory effects (Figure 3) (Zhang et al., 2022). Compared to current antirheumatic drugs, uPB-Exo offers superior targeting, enhancing therapeutic efficacy, reducing administration frequency, and minimizing side effects. The multifunctional nanozyme exhibits significant peroxidase and catalase-like catalytic activity, efficiently decomposing $H_2O_2$ into $O_2$ and $H_2O$ (Figure 3) (Zhang et al., 2022). Overall, uPB-Exo shows great promise in clinical RA diagnosis and treatment by effectively targeting and penetrating inflamed synovial and cartilage tissues, thus significantly improving joint health and reducing arthritis severity (Zhang et al., 2022).

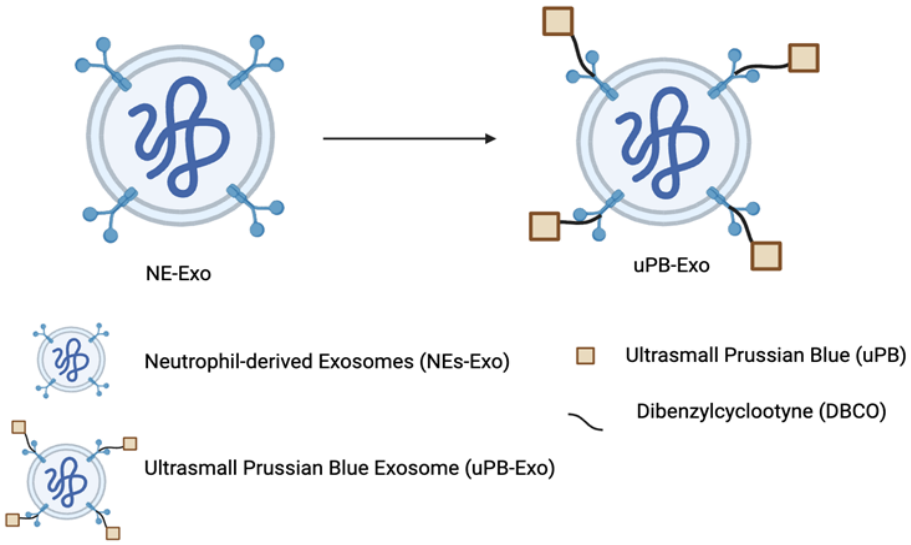


**Figure 2.** Diagram of uPB-Exo Nanozyme synthesis. uPB-Exo were developed by surface engineered neutrophil-derived exosomes (NEs-Exo) with sub-5 nm ultrasmall PBNPs (uPB) via click chemistry, a highly reliable chemical reaction that readily join two molecular entities together with excellent selectivity and high yield (Zhang et al., 2022).

Similarly, hydrogels have garnered substantial attention as effective vehicles for delivering bioactive substances such as drugs and stem cells in treating various disorders and reconstructing tissue functions (Zhao et al., 2022). However, hydrogel options for stem cell-based RA therapy are limited because most reported hydrogels focus solely on delivery functions without addressing hypoxia and ROS in the RA synovium (Zhao et al., 2022). Integrating hydrogels with nanozymes provides a more rational and targeted approach to decomposing ROS and sustaining oxygenation, thereby creating a suitable microenvironment to enhance cell viability and direct stem cell differentiation toward desired lineages (Zhao et al., 2022). To address these challenges, a nanozyme-reinforced hydrogel was developed as an $H_2O_2$-driven oxygenator to regulate stem cell behavior. This innovative hydrogel, derived from a dynamically cross-linked natural polymer and a catalase-mimic nanozyme, exhibits injectable, self-healing, and biocompatible (non-toxic and can coexist safely with living tissues) properties (Zhao et al., 2022). The cobalt oxide nanozyme was the hydrogel's building block, and ε-polylysine, rich in amino groups, was electrostatically assembled onto the MnCoO nanozyme surface to create ε-PLE@MnCoO nanoparticles. In experimental results, the $H_2O_2$ degradation capability was assessed with the addition of $H_2O_2$ to the nanozyme, significantly decomposing $H_2O_2$ and increasing

$O_2$ concentration (Figure 3). This demonstrates the nanozyme's catalytic durability and efficacy in creating an oxygen-rich environment (Zhao et al., 2022). For the *in vivo* study, a severe RA rabbit model was induced by subcutaneously injecting ovalbumin and Freund's adjuvant, with a cylindrical bone defect prepared on the distal femur tissues to mimic joint replacement surgery. As a result, the nanozyme scaffold reduced skin temperature and joint diameter, alleviating local inflammation and synovial hyperplasia (Zhao et al., 2022). Further analysis using immunofluorescence staining revealed that RA bone tissue treated with the nanozymes group displayed notably lower levels of green fluorescence, which represents the presence of ROS, compared to other treatments. This indicates the nanozyme-reinforced hydrogel's efficacy in reducing ROS levels and oxidative stress (Zhao et al., 2022). These findings underscore the nanozyme-reinforced hydrogel's superior antioxidation and hypoxia-relieving properties, highlighting its potential as an advanced stem cell delivery vehicle for managing hostile microenvironments and improving therapeutic outcomes in RA therapy.

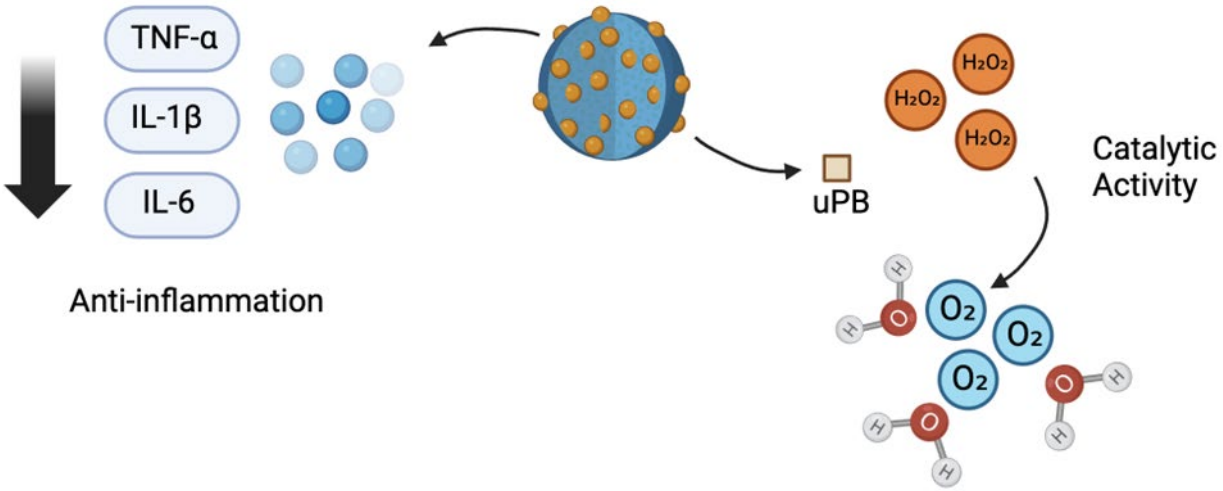


**Figure 3.** Nanozyme capabilities effectively targeted inflammation by reducing the presence of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) that were accumulated in inflamed joints and cartilage. Harbored ROS scavenging abilities and enzymatic qualities through the degradation of $H_2O_2$.

## Nanozyme-Encapsulated Drugs

While nanozymes themselves possess therapeutic capabilities for treating diseases like RA, their efficacy can be further enhanced by encapsulating them with additional drugs. One innovative approach involves disguising nanozymes within macrophage-derived microvesicles (MMV) for targeted delivery to inflammatory tissues. This strategy aims to prolong the circulation and persistence of nanozymes within inflamed joints by mimicking endogenous components, thereby reducing their elimination from the body (Jia et al., 2023). To synergize the anti-inflammatory effects of nanozymes, dexamethasone sodium phosphate (DSP), a commonly used glucocorticoid drug in RA treatment, was encapsulated within the hollow structure of nanozymes, like H–MnO2 (Jia et al., 2023). DSP is known to inhibit and downregulate pro-inflammatory cytokines such as TNF-α and IL-1β, which play crucial roles in RA pathogenesis (Jia et al., 2023). The study demonstrated that the H–$MnO_2$ nanozyme could effectively reprogram the metabolism of reactive oxygen species (ROS) like $O_2$– and $H_2O_2$, reducing intracellular ROS levels and downregulating the production of TNF-α and IL-1β (Jia et al., 2023). While the hollow, amorphous structure of the nanozyme enhanced its catalytic properties, it also increased cytotoxicity. However, this toxicity was significantly mitigated by coating the nanozyme with MMV, which improved biocompatibility and reduced immunogenicity due to its natural origin, in contrast to synthetic lipid coatings (Jia et al., 2023).The incorporation of MMV allowed for extremely efficient uptake

of the nanozymes by activated macrophages, leading to better therapeutic effects (Jia et al., 2023). Notably, the downregulation of ROS promoted the repolarization of activated macrophages to the anti-inflammatory M2 state, accelerating cartilage regeneration – a benefit not provided by conventional glucocorticoid analogs alone (Jia et al., 2023). Moreover, MMV, being extracellular vesicles, resembled cell membranes and acted as communication bridges between cells, further enhancing the effectiveness of the nanozymes (Jia et al., 2023). This study was the first to demonstrate the downregulation of TNF-α and IL-1β by messenger nanozymes on activated fibroblast-like synoviocytes and chondrocytes, attributed to the messenger function conferred by MMV in the inflammatory microenvironment of RA joints (Jia et al., 2023).

With a similar idea of doping nanozymes, concave-cubic rhodium nanozymes (Rh/SPX-HSA) were prepared by doping with sparfloxacin (SPX) and loading with human serum albumin (HSA) for RA treatment. Secreted protein acidic and rich in cysteine (SPARC) is a small glycoprotein, found to be highly expressed in the synovial fluid and joint tissues of collagen-induced arthritis (CIA) mice, which is abundant in cysteine (Zhou et al., 2023). Notably, SPARC has an inherent high affinity for albumin, which enhances the accumulation of HSA in inflammatory sites (Zhou et al., 2023). SPX, a fluoroquinolone antibacterial drug, exhibits notable sonodynamic properties and has been found to have greater retention in joint tissues following systemic administration (Zhou et al., 2023). With traditional ultrasound sonosensitizers increasing the production of ROS, sonodynamic therapy (SDT) is being researched as a safer option. This retention targets the abnormal proliferation of FLS in synovial tissue, effectively blocking joint inflammation. In comparison, rhodium (Rh) nanozymes with unconventional shapes, such as concave cubes, exhibit superior catalytic effects due to their high-energy facets. Rh nanoparticles display peroxidase (POD) and catalase (CAT) activities, generating radicals and alleviating hypoxia to kill synovial fibroblasts and inhibit angiogenesis ((Zhou et al., 2023). The cavitation effect occurring during SPX-sensitized sonodynamic therapy (SDT) further enhances Rh nanozyme activity, creating a mutually reinforcing SDT against RA (Zhou et al., 2023). The results demonstrated the highest POD-like activity for Rh/SPX-HSA under ultrasound conditions, confirming robust hydroxyl radical production (Zhou et al., 2023). Selective aggregation of Rh/SPX-HSA in inflamed joints of CIA mice was shown by stronger fluorescence signals compared to normal mice. The Rh/SPX-HSA group's fluorescence signal decayed slower than that of the Rh/SPX group, owing to SPARC's high affinity for HSA, confirming excellent targeting ability (Zhou et al., 2023). *In vivo*, fluorescence imaging revealed higher fluorescence intensity, correlating to increased ROS presence, in the inflamed paws of CIA mice compared to normal mice, consistent with the ex vivo fluorescent images. This finding further supported the selective accumulation of the nanozyme system in the inflamed joints (Zhou et al., 2023). While SPX, Rh-HSA, and Rh/SPX-HSA alone could not effectively prevent bone erosion, nanozyme-enhanced SDT with nanocarrier accumulation significantly reduced bone erosion (Zhou et al., 2023).

## Conclusion

While nanozyme therapeutics are an emerging field, numerous formulations have been designed and evaluated for rheumatoid arthritis treatment in recent years. Several innovative nanozyme systems were examined, including exosome-based nanozymes like uPB-Exo, nanozyme-reinforced hydrogels, and nanozyme-encapsulated drug formulations. These nanozyme approaches demonstrated superior therapeutic effects compared to conventional RA medications, such as improved targeting to inflamed joints, enhanced anti-inflammatory and antioxidant activity, and promotion of cartilage regeneration. Notably, the uPB-Exo nanozyme exhibited remarkable efficacy by selectively accumulating in activated synoviocytes, neutralizing pro-inflammatory factors, and alleviating oxidative stress in the arthritic joint environment. The multifunctional catalytic properties and deep tissue penetration of uPB-Exo highlight its potential as a comprehensive solution for managing RA. Further research is needed, but these pioneering nanozyme-based therapies hold significant promise for improving treatment outcomes and quality of life for rheumatoid arthritis patients, offering a more effective and safer alternative to traditional medications. More on this what makes uPB-Exo stand out among other nanozymes for RA treatment how do nanozymes like uPB-Exo reduce oxidative stress in

arthritic joints what are the key components of uPB-Exo that contribute to its effectiveness how do nanozymes like uPB-Exo penetrate deep into inflamed tissues what are the potential side effects of using uPB-Exo in RA patients.

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## References

Anselmo, A. C., & Mitragotri, S. (2019). Nanoparticles in the clinic: An update. *Bioengineering & Translational Medicine*, *4*(3), e10143. https://doi.org/10.1002/btm2.10143

Cooper, G. S., & Stroehla, B. C. (2003). The epidemiology of autoimmune diseases. *Autoimmunity Reviews*, *2*(3), 119–125. https://doi.org/10.1016/S1568-9972(03)00006-5

Delves Peter J. & Roitt Ivan M. (2000). The Immune System. *New England Journal of Medicine*, *343*(1), 37–49. https://doi.org/10.1056/NEJM200007063430107

Elkhalifa, S., et al. (2018). *Autoimmune Disease: Treatment* (pp. 1–11). https://doi.org/10.1002/9780470015902.a0001437.pub3

Firestein, G. S. (2003). Evolving concepts of rheumatoid arthritis. *Nature*, *423*(6937), 356–361. https://doi.org/10.1038/nature01661

Huang, Y., et al. (2019). Nanozymes: Classification, Catalytic Mechanisms, Activity Regulation, and Applications. *Chemical Reviews*, *119*(6), 4357–4412. https://doi.org/10.1021/acs.chemrev.8b00672

Jia, M., Ren, et al. (2023). Messenger Nanozyme for Reprogramming the Microenvironment of Rheumatoid Arthritis. *ACS Applied Materials & Interfaces*, *15*(1), 338–353. https://doi.org/10.1021/acsami.2c16458

Jiang, Z., et al. (2023). Fe-curcumin nanozyme-mediated immunosuppression and anti-inflammation in experimental autoimmune uveitis. *Biomaterials Research*, *27*(1), 131. https://doi.org/10.1186/s40824-023-00451-1

Li, D.-P., et al. (2023). A global assessment of incidence trends of autoimmune diseases from 1990 to 2019 and predicted changes to 2040. *Autoimmunity Reviews*, *22*(10), 103407. https://doi.org/10.1016/j.autrev.2023.103407

Liang, M., & Yan, X. (2019). Nanozymes: From New Concepts, Mechanisms, and Standards to Applications. *Accounts of Chemical Research*, *52*(8), 2190–2200. https://doi.org/10.1021/acs.accounts.9b00140

Mekuye, B., & Abera, B. (2023). Nanomaterials: An overview of synthesis, classification, characterization, and applications. *Nano Select*, *4*(8), 486–501. https://doi.org/10.1002/nano.202300038

Sahu, T., et al.(2021). Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. *Journal of Drug Delivery Science and Technology*, *63*, 102487. https://doi.org/10.1016/j.jddst.2021.102487

Shah, B. (2023, February). *Rheumatoid Arthritis*. https://rheumatology.org/patients/rheumatoid-arthritis

Smith, J. B., & Haynes, M. K. (2002). Rheumatoid Arthritis—A Molecular Understanding. *Annals of Internal Medicine*, *136*(12), 908–922. https://doi.org/10.7326/0003-4819-136-12-200206180-00012

Sudres, M., et al. (2018). Pathophysiological mechanisms of autoimmunity. *Annals of the New York Academy of Sciences*, *1413*(1), 59–68. https://doi.org/10.1111/nyas.13560

Wang, L., et al. (2015). Human autoimmune diseases: A comprehensive update. *Journal of Internal Medicine*, *278*(4), 369–395. https://doi.org/10.1111/joim.12395

Weyand, C. M., & Goronzy, J. J. (2021). The immunology of rheumatoid arthritis. *Nature Immunology*, *22*(1), 10–18. https://doi.org/10.1038/s41590-020-00816-x

Yang, W., et al. (2021). Nanozymes: Activity origin, catalytic mechanism, and biological application. *Coordination Chemistry Reviews*, *448*, 214170. https://doi.org/10.1016/j.ccr.2021.214170

Zhang, L., et al.(2022). Nanoenzyme engineered neutrophil-derived exosomes attenuate joint injury in advanced rheumatoid arthritis via regulating inflammatory environment. *Bioactive Materials*, *18*, 1–14. https://doi.org/10.1016/j.bioactmat.2022.02.017

Zhao, Y., et al. (2022). Nanozyme-reinforced hydrogel as a H2O2-driven oxygenerator for enhancing prosthetic interface osseointegration in rheumatoid arthritis therapy. *Nature Communications*, *13*(1), 6758. https://doi.org/10.1038/s41467-022-34481-5

Zhou, F., et al. (2023). Redox Homeostasis Strategy for Inflammatory Macrophage Reprogramming in Rheumatoid Arthritis Based on Ceria Oxide Nanozyme-Complexed Biopolymeric Micelles. *ACS Nano*, *17*(5), 4358–4372. https://doi.org/10.1021/acsnano.2c09127