

High-entropy nanozymes: a frontier toward next-generation high-performance nanozymes

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1. Introduction

Nanozymes are a revolutionary class of artificial enzymes that combine nanomaterial properties with enzyme-like catalysis. Their emergence has reshaped catalytic science, bridging the gap between organic and inorganic catalysts and transforming paradigms in enzymology^[1]. This transformative potential has earned nanozymes high-profile recognition, including being named a “Top 10 Emerging Technology” by IUPAC and a “Top 10 Chemistry and Materials-Science Frontier” by the Chinese Academy of Sciences in 2022. Advances in nanotechnology, analytical chemistry, and computation have enabled the construction of diverse nanozymes. Compared to natural enzymes, they offer advantages such as tunable structures, scalable synthesis, low cost, easy modification, high stability, and stimuli-responsive activity. Scientific consensus views nanozymes not only as a powerful complement but also as a potential successor to natural enzymes in future applications^[2]. With their ability to provide efficient, stable, and economical catalytic solutions, nanozyme research is now in an era of deep interdisciplinary integration, poised to tackle major challenges in biomedicine, environmental monitoring, and green chemistry^[3].

Recent advances in nanozyme development have seen a rational evolution from conventional nanomaterials to ultrafine nanoparticles, sub-nanometer clusters, and ultimately to single-atom catalysts^[4,5]. Conventional nanomaterials face limitations like low-active site density and structural heterogeneity, driving the evolution toward single-atom catalysts for maximal atomic

efficiency. However, their reliance on a single metal site restricts catalytic tunability. This has spurred the emergence of high-entropy alloys, which incorporate multiple principal elements into a solid-solution phase. This design creates diverse neighboring active sites and enables synergistic effects. These effects collectively optimize electronic structure and intermediate adsorption, allowing high-entropy nanozymes (HEAzymes) to overcome the limitations of simpler catalysts and represent a true paradigm shift in nanozyme design^[6]. Because their conceptual introduction in 2004, high-entropy alloys, defined as solid solutions of 5 or more principal metallic elements in near-equimolar ratios (5%–35% each), have garnered significant interest. Their unique properties stem from 4 core effects: high configurational entropy, severe lattice distortion, sluggish diffusion, and a synergistic “cocktail” effect. Their exceptional performance stems from four mutually reinforcing pillars: the high configurational entropy that thermodynamically locks single-phase solid solutions and permits massive supersaturation of otherwise immiscible elements; the severe lattice distortion that generates a rugged energy landscape, pinning dislocations, deflecting cracks and continuously re-forming an element-rich passivation film, thereby delivering high strength, superior fracture toughness and markedly retarded corrosion; the sluggish multielement diffusion that exponentially raises hopping barriers, suppressing creep, grain growth and oxidation by orders of magnitude; and the synergistic “cocktail” effect in which 5 or more principal elements collectively tune adsorption energies to the Sabatier optimum, shift the *d*-band center and accelerate charge transfer, unleashing record catalytic activity.

To date, HEAzymes have been developed to effectively mimic natural enzymatic activities, such as peroxidase (POD) and superoxide dismutase (SOD). Their high-entropy framework not only provides exceptional structural stability but also serves as a versatile platform for fine-tuning catalytic performance through compositional design. Owing to these advantageous properties, HEAzymes have shown considerable promise across diverse fields, including tumor immunotherapy, anti-inflammatory tissue regeneration, pathogen and biomarker detection, and environmental pollutant degradation. Considering these advances, this perspective reviews recent progress in the synthesis methods, characterization techniques, and practical applications of HEAzymes (Figure 1).

2. Synthetic methods for HEAzymes

The investigation of synthesis methods for HEAzymes serves as a fundamental prerequisite and a critical pathway for technological advancement in this field. The synthesis is broadly classified into “top-down” and “bottom-up” approaches. Top-down methods start with bulk high-entropy materials and break

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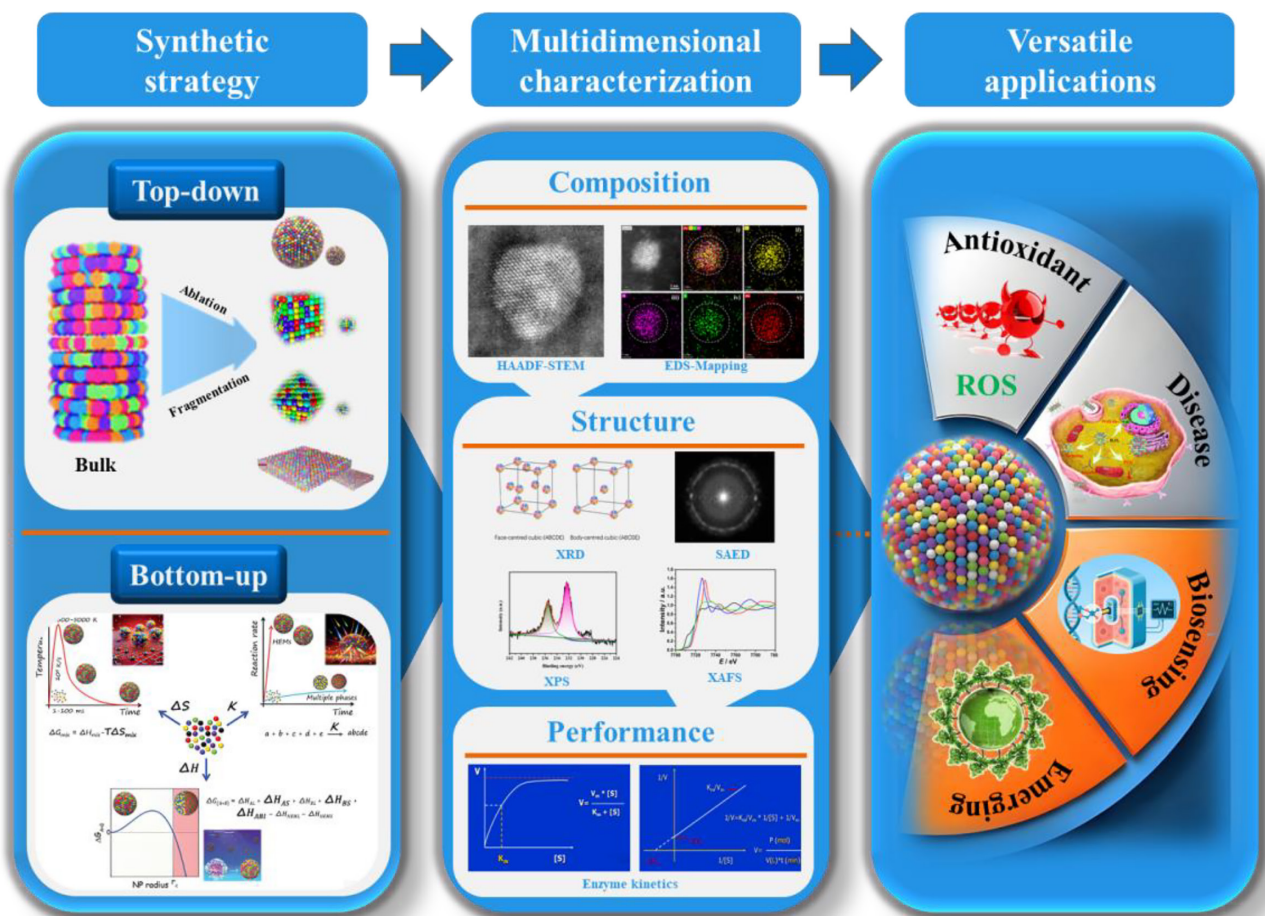


Figure 1. Synthesis, characterization, and applications of HEAzymes.

them down into nanostructures using physical or chemical energy, offering the advantage of relatively simple processes^[7]. In contrast, bottom-up methods construct nanoparticles from molecular precursors via chemical reactions, which more readily yield well-dispersed isolated particles and allow for fine control over size, shape, composition, and crystal structure^[8]. In this subsection, the top-down and bottom-up synthesis methods for HEAzymes are summarized.

2.1 Top-down methods

The top-down synthesis pathway primarily involves the physical or chemical “fragmentation” of bulk materials. Among the prevalent top-down physical fabrication techniques, each method exhibits distinct characteristics and inherent limitations^[9]. Ball milling accomplishes alloying and grain refinement via high-energy mechanical collisions, valued for its operational simplicity, yet it offers inadequate control over final particle size and morphology. Dealloying produces porous nanoframes through the selective dissolution of specific elements from a precursor alloy, although precise tailoring of porosity and composition remains challenging. Arc or spark discharge employs an electrode evaporation–condensation mechanism to rapidly synthesize nanoparticles with tunable compositions; however, the resulting particles generally exhibit large dimensions and a broad size distribution. Laser ablation utilizes ultrashort pulses to irradiate a target, enabling the generation of ultrafine particles, but its scalability is hindered by low yield and substantial equipment costs. Sputter deposition achieves atomic deposition onto a substrate through ion bombardment, allowing precise control over composition and dimensions, yet it necessitates a

vacuum environment and seldom yields well-dispersed, isolated nanoparticles directly. In summary, top-down approaches often lack the precision required to control the size, morphology, and surface properties of isolated nanoparticles, frequently leading to agglomerated nanocrystalline grains or bulk structural powders.

2.2 Bottom-up methods

The bottom-up strategy starts from precursors such as metal salts or complexes, enabling precise control through the chemical “self-assembly” of nanoparticles in solution or gas phases^[10]. The carbothermal shock method fixes the high-entropy phase via millisecond-level Joule heating and rapid quenching, producing small particles around 5 nm but requiring a conductive substrate. The aerosol droplet method uses atomized droplets as microreactors for continuous pyrolysis, favoring scalability but typically yielding polycrystalline products. Sonication-assisted and microwave-assisted wet-chemical methods promote reduction and nucleation through cavitation effects or selective heating, respectively; they are operationally simple but may compromise particle uniformity. Electrodeposition achieves co-deposition of metal ions by modulating voltage, allowing precise compositional design but being limited to conductive substrates. Pyrolysis/calcination obtains supported particles in one step by high-temperature decomposition of precursor-support mixtures, albeit with high energy consumption and a tendency for sintering. Solvothermal/hydrothermal methods facilitate reduction and crystallization in a sealed, high-pressure environment, effectively tuning morphology and crystal phase, but the process cannot be interrupted once initiated. Colloidal chemical

synthesis offers the most flexible and controllable pathway by precisely regulating nucleation and growth kinetics in solution, enabling the customized fabrication of nanoparticle size, morphology, composition, and even metastable structures.

Although the synthesis of HEAzymes has established 2 major strategic systems, it still faces challenges such as precise control, scalability, and sustainability. Future efforts should focus on developing hybrid synthesis and external-field regulation technologies to achieve atomic-level precision in fabrication, expanding new component systems involving nonprecious metals and defect engineering, and integrating machine learning for inverse design. Additionally, advancing continuous green processes and in situ monitoring will facilitate the transition toward a new stage of customizable, high-performance rational manufacturing, thereby supporting their broad applications.

3. Characterization methods for HEAzymes

Following the synthesis of HEAzymes, comprehensive characterization of their physicochemical properties is essential to confirm whether they satisfy the structural and compositional criteria for classification as HEAzymes. The validation of a synthesized nanomaterial as a HEAzyme depends on systematic verification of its composition, phase structure, elemental distribution, and relevant functional properties. The core validation criteria are as follows: (1) compositionally, the material must contain at least 5 principal metallic elements, each with an atomic percentage ranging from 5% to 35%; (2) structurally, it should form a single solid-solution phase; and (3) in terms of elemental distribution, homogeneous mixing at the nanoscale without significant phase segregation should be achieved^[11]. This section reviews the analytical methods and corresponding evidence used to verify these criteria.

3.1 Compositional characterization

Compositional characterization aims to verify the multiprincipal-element, near-equi-atomic composition of the material^[12]. Bulk analysis techniques (e.g., ICP-MS, AES) provide the average chemical composition, while microscale analysis (e.g., point, line, and area scans via SEM/TEM-EDS) reveals local compositional information. Among these, High-Angle Annular Dark-Field Scanning Transmission Electron Microscope coupled with EDS mapping allows for the intuitive confirmation of elemental homogeneity at the nanoscale. For ultimate resolution, atom

probe tomography can resolve 3D elemental distributions at the atomic scale, serving as a definitive technique for assessing the randomness of the solid solution.

3.2 Structural characterization

The core objective of structural characterization is to verify the single-phase solid solution and the “high-entropy effect” at the crystallographic level^[13]. Key methods include XRD for determining the single-phase crystal structure, where significant peak broadening serves as direct evidence of lattice distortion; electron diffraction and HRTEM for confirming the single-phase nature at the microscale and for observing distortions and defects; synchrotron radiation/neutron diffraction for precise analysis of atomic occupancy and local structural distortions; and APT for identifying short-range order at the atomic scale. Collectively, these analyses elucidate the essential features of HEAzymes: a single-phase solid solution and severe lattice distortion.

3.3 Performance characterization

Performance characterization provides corroborating evidence for the high-entropy nature by evaluating the material’s unique functional profile, primarily covering 2 aspects: Catalytic Performance, assessed through enzyme-like kinetics, multienzymatic activity profiling, and electrochemical tests to verify the “cocktail effect” and enhanced activity; and Stability and Durability, evaluated via thermal analysis, exposure tests under extreme conditions (pH/salinity), and cycling experiments to reveal the sluggish diffusion effect and structural robustness. Performance characterization serves as the crucial link connecting compositional and structural features to ultimate application value^[14].

Although the current characterization system for HEAzymes is relatively comprehensive, it must evolve to meet the increasingly complex demands of material design and application. Future efforts should focus on establishing an integrated characterization paradigm that is multiscale, multimodal, dynamic, and in situ. This includes, for example, integrating multisource data with machine learning to construct quantitative structure–activity relationship maps; developing real-time, operation-condition dynamic characterization techniques; establishing standardized evaluation systems tailored to different application scenarios; and promoting the construction of high-throughput automated characterization platforms. These advances will deepen scientific understanding and accelerate the translation of materials into practical applications.

Table 1

The core feature, design, advantages, challenges, and relationship of HEAzymes with other nanozymes.

Feature dimension	Conventional nanozymes	SAzymes	HEAzymes
Core Feature	Intrinsic catalytic activity of the material, relying on surface chemistry.	Atomically dispersed metal active centers, maximizing atomic utilization.	Multiprincipal-element (≥ 5) mixing in near-equi-atomic ratios, pursuing a synergistic “cocktail effect.”
Design	Initially driven by empirical discovery and screening.	Rational design, precisely tailoring the coordination environment of metal centers to mimic natural enzymes.	High-throughput exploration of complex compositional space, utilizing AI and robotics for multiobjective optimization.
Advantages	Relatively simple preparation; well-studied catalytic mechanisms.	High catalytic efficiency; well-defined structure; facilitates mechanistic studies.	Infinitely tunable composition and properties; potential to surpass single-component materials.
Challenges	Low-active site density; catalytic efficiency and selectivity often inferior to natural enzymes.	Difficult synthesis; challenges with stability under high temperatures or harsh environments.	Complex synthesis control; extremely intricate structure–property relationships; reliant on advanced algorithms for design.
Relationship	The dominant material system in current applied research.	An exemplary achievement of the rational design paradigm, not a replacement for the former.	A future-oriented new material system, developing in parallel with single-atom nanozymes.

HEAzymes, high-entropy nanozymes; SAzymes, single-atom nanozymes.

4. Application progress of HEAzymes

As shown in Table 1, the development of nanozymes exhibits a progression from conventional materials to rationally designed systems. Conventional nanozymes, relying on intrinsic material properties, remain the mainstream for applications. Single-atom nanozymes, featuring atomically dispersed active sites, provide exceptional efficiency and well-defined structures for mechanistic exploration. Representing an emerging paradigm, HEAzymes leverage multielement synergy and AI-driven design to achieve unprecedented compositional tunability, advancing on a complementary trajectory to single-atom nanozymes. These characteristics provide a versatile platform for diverse applications^[15]. To enable scientists in related fields to more rapidly understand and utilize HEAzymes, thereby promoting advancements in this area, this section briefly discusses their progress in antioxidant therapy, disease treatment, biosensing, and other emerging fields.

4.1 Antioxidant

HEAzymes show significant potential in antioxidative research due to multielement synergy and tunable electronic structures. They can mimic natural antioxidant enzymes (e.g., SOD, CAT, GPX) to efficiently scavenge ROS/RNS and regulate oxidative stress pathways such as ferroptosis^[16]. Through defect engineering or doping, their catalytic activity and electron transfer can be precisely modulated, enabling synergistic or dynamically switchable antioxidant functions. This programmability offers a powerful platform for intervening in oxidative stress-related diseases.

4.2 Disease treatment

HEAzymes leverage their unique structural advantages to outperform conventional nanozymes. For anti-infection therapy, enhanced POD-like activity converts endogenous H_2O_2 into toxic radicals, improving bactericidal efficiency. In chronic wound healing, their multienzyme mimicry clears diverse ROS, breaking the oxidative stress cycle and accelerating tissue repair when integrated with biomaterials^[17]. In oncology, they respond to the tumor microenvironment, inducing synergistic cell death via mechanisms like Cu proptosis. Surface modification enables targeted delivery, advancing precision therapy. For neurological inflammation, they block the oxidative-inflammatory cascade by regulating pyroptosis, highlighting their role as a transformative platform for next-generation intelligent therapeutics.

4.3 Biosensing

HEAzymes offer unique value in biosensing by combining the stability and functional of nanomaterials with enhanced catalytic properties. They overcome natural enzyme limitations and enable high-performance, multifunctional sensing platforms. Key advances include: combined detection and degradation of environmental pollutants; enhanced sensitivity in portable diagnostics; discriminative multi-biomarker detection; and logic-gate controlled specific imaging^[18]. Despite challenges in efficiency, mechanism, and standardization, their advantages in stability, signal amplification, and intelligent detection chart a promising path for next-generation biosensing technologies.

4.4 Other emerging areas

In emerging fields, HEAzymes provide novel tools for regulating complex biochemical processes through multienzyme mimicry. Their stability under extreme conditions supports applications in environmental biotechnology, deep-sea, and space

exploration. Tunable catalytic activity enables smart responses to specific microenvironments, advancing precision medicine and drug delivery. In green technology, multielement synergy enhances catalytic efficiency and reduces energy consumption, paving the way for sustainable manufacturing and chemical processes^[19,20].

5. Future research prospects

The field of nanozymes was inaugurated in 2007, and its formal establishment as an independent, interdisciplinary discipline, nanozymology, was marked by the publication of the seminal treatise “Nanozymology” in 2020. The concept of HEAzymes was first proposed in 2023. The strategic importance of this field has been further emphasized by the World Economic Forum, which included nanozymes in its 2025 list of “Top Ten Emerging Technologies.”

Despite the rapid progress in recent years, research on HEAzymes remains in its early stages and faces several critical challenges. Key limitations include synthetic difficulties, such as limited controllability and scalability; catalytic performance that still falls short of natural enzymes in terms of activity and selectivity; and an incomplete mechanistic understanding of phenomena such as the “cocktail effect” and its role in synergistic catalysis. The absence of standardized evaluation protocols further hinders progress. A paradigm shift from empirical exploration to rational design is now underway. This new approach integrates artificial intelligence and high-throughput screening for predictive design, employs advanced synthesis techniques to improve uniformity, and utilizes in situ characterization coupled with machine learning to elucidate dynamic catalytic mechanisms. Performance assessment must also evolve from simple activity tests to multidimensional evaluation using advanced biological models like organoids and organ-on-a-chip. Future translation of this technology depends on establishing universal standards, exploring novel material systems via microfluidics for high-throughput platforms, engineering HEAzymes for enhanced selectivity and biosafety, and expanding their applications in biomedicine and environmental catalysis. Ultimately, the development of “digital platforms” for fostering of deep interdisciplinary collaboration will be crucial to bridge the gap between foundational research and practical applications^[21].

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Conflicts of interests

The authors declare that they have no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Meng-Qi He and Yuting Gong designed the structure and wrote the manuscript with inputs from all authors. Ran Wang, Ping Liu, Bing Fang, Yixuan Li and Pengjie Wang investigation, project administration, resources. Hong-bin Sun, Huiyuan Guo, Qionglin Liang, Fazheng Ren, and Yongjian Ai revised the manuscript, funding acquisition, conceptualization, and supervision. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

References

- [1] Zhang R, Jiang B, Fan K, et al. Designing nanozymes for in vivo applications. *Nat Rev Bioeng*. 2024;2:849–868.
- [2] Zhang Y, Wei G, Liu W, et al. Nanozymes for nanohealthcare. *Nat Rev Method Primer*. 2024;4:36.
- [3] Ai Y, Hu Z, Liang X, et al. Recent advances in nanozymes: from matters to bioapplications. *Adv Funct Mater*. 2022; 32: 2110432.
- [4] Sun Y, Dai S. Synthesis of high-entropy materials. *Nat Synth*. 2024;3:1457–1470.
- [5] Luo M, Xie Z, Li H, et al. Physics-informed, dual-objective optimization of high-entropy-alloy nanozymes by a robotic AI chemist. *Matter*. 2025;8:102009.
- [6] Ai Y, He M, Sun H, et al. Ultra-small high-entropy alloy nanoparticles: efficient nanozyme for enhancing tumor photothermal therapy. *Adv Mater*. 2023; 35: 2302335.
- [7] Kar N, Skrabalak SE. Synthetic methods for high-entropy nanomaterials. *Nat Rev Mater*. 2025;10:638–653.
- [8] He M, Ai Y, Hu W, et al. Recent advances of seed-mediated growth of metal nanoparticles: from growth to applications. *Adv Mater*. 2023;35:2211915.
- [9] Cao G, Liang J, Guo Z, et al. Liquid metal for high-entropy alloy nanoparticles synthesis. *Nature*. 2023;619:73–77.
- [10] Yao Y, Huang Z, Xie P, et al. Carbothermal shock synthesis of high-entropy alloy nanoparticles. *Science*. 2018;359:1489–1494.
- [11] Ai Y, Wang Z, Shi W, et al. Atomic-level high-entropy nanozymes enable remarkable endogenous targeted catalysis and enhancing tumor photothermal therapy. *Adv Mater*. 2025;37:2502322.
- [12] Yang L, He R, Chai J, et al. Synthesis strategies for high entropy nanoparticles. *Adv Mater*. 2025; 37: 2412337.
- [13] Moniri S, Yang Y, Ding J, et al. Three-dimensional atomic structure and local chemical order of medium- and high-entropy nanoalloys. *Nature*. 2023;624:564–569.
- [14] Feng J, Yang X, Du T, et al. Transition metal high-entropy nanozyme: multi-site orbital coupling modulated high-efficiency peroxidase mimics. *Adv Sci*. 2023;10:e2303078.
- [15] Xue P, Chang Y, Wang C, et al. High-entropy antibacterial materials. *MedMat*. 2025;10.1097/mm9.0000000000000026.
- [16] Ding C, Min J, Tan Y, et al. Combating atherosclerosis with chirality/phase dual-engineered nanozyme featuring microenvironment-programmed senolytic and senomorphic actions. *Adv Mater*. 2024;36:2401361.
- [17] Li D, Ha E, Zhu Y, et al. Alternating current pre-treatment enhances multi-enzymatic activity of high-entropy alloy nanozymes that regulate metabolism for effective tumor immunotherapy. *Nat Commun*. 2025;16:11542.
- [18] Lin H, Ke L, Wang S, et al. DFT-guided design of a multi-enzyme mimetic high-entropy nanozyme for cascaded glutathione detection and point-of-care testing. *Adv Sci*. 2025;13:e15765.
- [19] Wang C, Yuan F, Yan Z, et al. High entropy 2D layered double hydroxide nanosheet toward cascaded nanozyme-initiated chemodynamic and immune synergistic therapy. *J Am Chem Soc*. 2025;147:136–148.
- [20] Du Y, He Z, Chen C, et al. Pathogenesis-guided nanozymes: from design to therapy for gastrointestinal inflammation. *MedMat*. 2025.
- [21] Yao Y, Dong Q, Brozena A, et al. High-entropy nanoparticles: synthesis-structure property relationships and data-driven discovery. *Science*. 2022;376:eabn3103.

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