Acupuncture and Herbal Medicine

Herbzyme: uncovering a secret of traditional Paozhi-processing and advancing the modernization of traditional Chinese medicine through nanotechnology, sustainability, and AI

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Originally conceptualized in 2021, herbzyme is defined as a class of catalytic nanoscale assemblies generated by traditional Chinese medicine (TCM) processing (Paozhi) with potent enzyme-mimicking or coenzymatic activities, providing a mechanistic explanation for traditional Paozhi practices through modern nanotechnology[1]. This Perspective distinguishes herbzyme from hydrothermally synthesized herbal carbon dots, conventional synthetic nanozymes, and native protein enzymes, and discusses the unresolved criteria required to establish herbzyme as a distinct scientific entity. We focus on four questions: how processing conditions govern herbzyme formation; how catalytic diversity and structural mechanisms should be interpreted; how nanoassembly-dependent catalysis can be distinguished from the pharmacological effects of retained phytochemicals; and which approaches to standardization, safety assessment, manufacturing, and enabling technologies are most relevant to translation. Speculative concepts, including quantum effects and AI-assisted design, are considered future hypotheses or tools rather than established mechanisms.

Establishing a standardized definition of herbzyme

Conflating herbzyme with hydrothermally synthesized carbon-dot nanozymes obscures the distinctive value of atmospheric-pressure TCM processing-derived catalysis

The term "herbzyme" (herb + enzyme) was first introduced in 2021 to describe nanoscale assemblies generated during herbal processing that exhibit enzymatic or coenzymatic activity[1]. However, the literature has often grouped these processing-derived catalytic nanoparticles with carbon-dot nanozymes produced by high-temperature, high-pressure hydrothermal synthesis. Thus, such categorization may obscure important phenotypic differences between the two systems. On the one hand, hydrothermally synthesized carbon dots rely on intensive thermal treatment, which may break down a substantial proportion of native herbal metabolites and compounds. On the other hand, herbzyme can be formed under atmospheric-pressure processing conditions and may retain bioactive phytochemicals. Unlike native protein–based herbal enzymes and chemically synthesized nanozymes, herbzyme is proposed to arise from rearrangements induced during Paozhi-processing[1]. Although functional intersection exists, including superoxide dismutase (SOD)–like and peroxidase-like activities, differences in processing conditions and retained phytochemical profiles in part support reconsideration of herbzyme within a distinct conceptual framework. However, standardized criteria for herbzyme yield, catalytic active sites, and major components remain elusive.

Standardizing gradient processing temperatures to define quantitative boundaries among herbzyme, carbon dots, and quantum dots

Currently, a high-priority research objective should be constructing a temperature-gradient Paozhi experimental matrix spanning routine temperatures (approximately 100°C), moderate thermal processing (180°C–200°C), and more extreme synthesis conditions (>220°C), as well as other Paozhi gradients to explore the best methods to establish a standard. Using these methods, researchers could rigorously quantify nanoparticle morphology, surface functional groups, catalytic kinetic parameters, and residual phytochemical content to help establish quantitative criteria for the distinction of herbzyme. Traditional Paozhi adjuvants, including wine, vinegar, honey, and brine, can also alter the chemical composition and pharmacological properties of herbal materials and enzyme activities[2]. A recent study indicates that variations in processing temperature and duration can generate particles with distinct

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enzyme activities and differential effects on cell signaling and ferroptosis-related responses[3]. In detail, Aicao/honey processing at different temperatures generates particles with distinct physicochemical properties and peroxidase- and phosphatase-like activities[3]. Whether other processing adjuvants similarly modulate herbzyme nanoassembly and catalytic selectivity remains unknown.

Evidence for quantum-confinement–related optical characteristics in Paozhi-derived herbzyme is unclear. By contrast, hydrothermally synthesized carbon dots exhibit size-dependent optical properties[4]. Systematic comparisons across processing temperatures, pressures, and particle-size ranges are therefore needed to determine whether a meaningful physicochemical boundary should be established among herbzyme, carbon dots, and quantum-dot–like materials (Table 1). These studies should also investigate nanoscale toxicity alongside potential advantages such as cellular uptake and access to subcellular compartments.

Building a terminology consensus for processing-induced polymeric nanoassemblies and herb-derived protein enzymes within a broader herbzyme research framework

A consistent definition is essential for the herbzyme field. Catalytic polymeric nanoparticles generated from traditional Paozhi processing may reasonably be discussed within the herbzyme framework. However, the status of unprocessed herb-derived native protein enzymes and laboratory-generated pressurized hydrothermal nanomaterials requires clearer conceptual boundaries (Figure 1). Standardized terminology would reduce inconsistent naming across the literature and support the development of a coherent research framework spanning sustainability and future AI-assisted discovery. Herb-derived protein enzymes may be considered to be included within a broader herbzyme research discipline because plant-derived enzymes have been studied for therapeutic applications, such as enzyme replacement therapy for exocrine pancreatic insufficiency[5].

Interpreting the relationship between herbzyme catalytic diversity and pharmacologically relevant enzyme-like activities

Extreme thermostability and pH tolerance are phenotypic features, but the range of protein-enzyme–like activities mimicked by herbzyme remains limited

Thermal processing can promote structural rearrangement of herbal nanoassemblies, causing them to exhibit phosphatase-, lyase-, and antioxidant-like catalytic activities. In the original herbzyme study, several processed herbs showed higher phosphatase-like activity than their unprocessed controls, and peroxidase- and lyase-like activities were identified in the processed herbal assemblies[1,6]. Compared with protein-based enzymes, herbal particle assemblies may retain catalytic activity across broader physicochemical conditions. However, it is difficult for herbal nanoparticles to mimic the structural and functional diversity of highly evolved native protein–based enzymes. How processing standards determine catalytic diversity and specificity remains a central unsolved problem.

A further hypothesis is that catalytic profiles may eventually be related to TCM syndrome patterns. For example, SOD-like activity could be explored in blood-stasis patterns associated with oxidative stress, whereas phosphatase-like activity could be investigated in blood-stasis–related patterns involving dysregulated kinase signaling. Such catalytic profile-syndrome matching remains conceptual and requires direct experimental and clinical validation.

Table 1

Comparison of herbzyme with related catalytic systems

Feature	Processing-derived herbzyme	Hydrothermal carbon dots	Conventional nanozymes	Herb-derived protein enzymes
Origin	Herbal materials subjected to traditional Paozhi/processing	Herbal precursors subjected to thermal/hydrothermal carbonization	Artificially synthesized nanomaterials	Naturally occurring herb-derived proteins
Formation	Processing-induced self-assembly	Thermal/hydrothermal synthesis, often under elevated temperature/pressure	Chemical or physical synthesis	Biological biosynthesis
Catalytic characteristics	Enzyme-like catalytic activity	May exhibit enzyme-like catalytic activity	Enzyme-mimicking catalysis	Native protein enzymatic catalysis
Association with herbal phytochemicals	May retain herb-derived phytochemical constituents	Variable and synthesis-dependent	Generally absent	Derived from the herbal biological matrix
Active-site definition	Not yet standardized	Often heterogeneous or incompletely defined	Surface/metal catalytic sites may be characterized	Structurally defined protein active sites
Current major challenge	Definition, mechanism, quality control, and translation	Structure-activity relationship and compositional control	Catalytic specificity and biosafety	Stability, isolation and production

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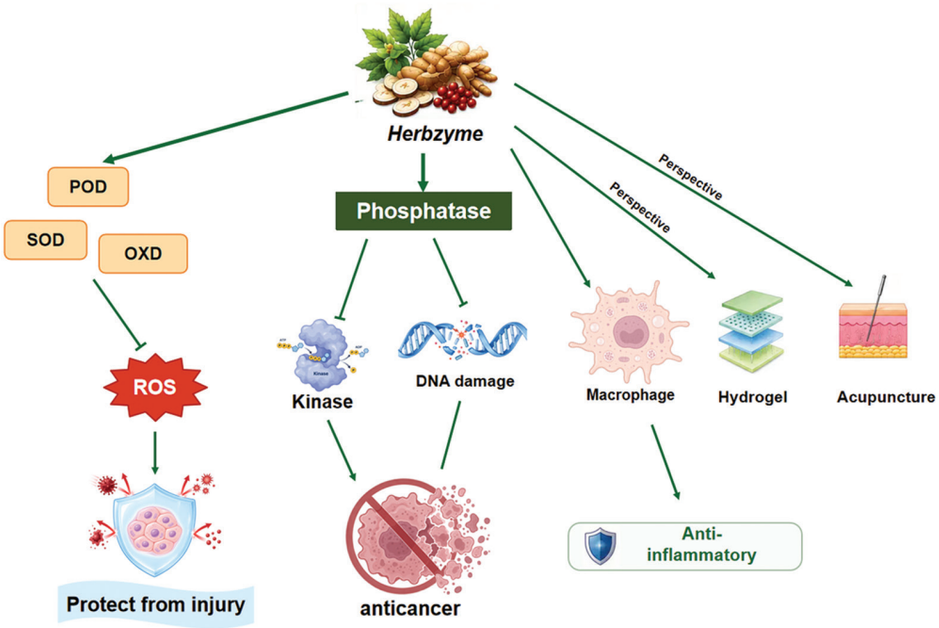


Figure 1. Conceptual framework of herbzyme with its reported functions and future perspectives design. Herbzyme-induced cell signaling, Paozhi processing, herbzyme activity, and future directions are indicated. OXD: Oxidase; POD: Peroxidase; ROS: Reactive oxygen species; SOD: Superoxide dismutase.

Low-temperature stability remains an understudied issue for pharmaceutical development

Stability is essential for herbzyme to progress to a reproducible pharmaceutical material. Recently, a study reported that low-temperature-adapted single-atom nanozymes can retain catalytic activity under cold-chain conditions, but comparable data are not yet available across herbzyme subtypes[7]. Future studies should include quantifying particle-size distribution, batch-to-batch reproducibility, standardized catalytic activity units, and activity retention under defined storage conditions, drawing on established principles learned from nanozyme activity assays[8]. Longitudinal assessment of catalytic decay and structural changes will be necessary to define practical storage specifications.

Structural catalysis: polymeric self-assembly challenges the classical lock-and-key model and motivates further mechanistic investigation

Herbzyme is proposed to be hierarchically self-assembled polymeric nanoscale clusters generated during Paozhi, rather than isolated monomeric phytochemicals. Atomic force microscopy has revealed diverse morphologies in processed *Rhizoma Polygonati*, *Lycium chinense*, and other herbal materials, but high-resolution information on active-site-substrate interactions remains lacking[1,9–10]. Ethylenediaminetetraacetic acid (EDTA)-sensitive activity and quantum-mechanical calculations in early herbzyme studies suggest that metal ions, surface hydroxyl groups, and deprotonated sugar alkoxide groups may contribute to phosphatase-like enzyme activity[1]. The preliminary results suggest that the classical protein lock-and-key model may be insufficient to establish the theory of herbzyme in catalysis.

Whether quantum effects contribute to catalytic turnover in herbzyme remains an intriguing but untested hypothesis. Structural characterization of catalytic sites, rigorous kinetic analysis, and quantum mechanisms should be evidenced in future studies.

Applying principles of enzyme evolution to develop bioinformatics workflows for high-throughput screening of novel herbzyme catalytic subtypes

Experimentally reported herbzyme activities include phosphatase-like, peroxidase-like, lyase-like, SOD-, catalase-, and other enzyme-mimicking activities[1,6,10]. In high-throughput screening studies, evolutionary and bioinformatics approaches may help prioritize candidate catalytic types. A phylogenetic comparison of natural enzymes previously predicted peroxidase and lyase as conserved catalytic classes and was followed by experimental identification of lyase-like activity in *Rhizoma Polygonati* and peroxidase-like activity in *Lycium chinense* assemblies[6].

In the longer run, integrating processing parameters, phytochemical composition, enzymatic types and activities could support data-driven prediction. Protein-focused AI tools such as AlphaFold and emerging

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enzyme design methods provide conceptual inspiration. However, herbzyme-specific models will require datasets and experimental validation before rational design becomes feasible[11–12].

Critical viewpoint: the dual contributions of nanocatalysis and retained herbal phytochemicals redefine the modern interpretation of TCM processing

Single-component nanozymes cannot fully reproduce the multitarget therapeutic potential of composite herbzyme formulations

Herbzyme may exert a dual pharmacological effect through nanostructure-dependent enzymatic catalysis and retained native herbal small molecules. For example, a galangin-derived natural-product nanozyme has been shown to exert antitumor effects through reactive oxygen species (ROS)-associated mitogen-activated protein kinase (MAPK) signaling in hepatocellular carcinoma[13]. Another example is that a combined *Rhizoma Polygonati* and *Lycium chinense*-derived herbzyme complex has been shown to inhibit prostate cancer cell proliferation through G0/G1 cell-cycle arrest, targeting phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) signaling, and altering androgen-related signaling, which suggests a multitarget effect[14]. Future therapeutic studies should explicitly separate purified herbzyme nanostructures from herbal compound fractions. Such fractionation is necessary to distinguish nanoassembly-dependent enzyme function from the herbal compound effect[1]. Controlled comparative experiments could then quantify the relative contributions of catalytic nanoassemblies and phytochemicals, thereby providing a more rigorous mechanistic basis for interpreting the dual therapeutic effects.

Key unresolved mechanistic gap: distinguishing phytochemical bioactivity from nanoassembly-dependent enzyme activity

A *Coptis chinensis*–derived SOD-mimetic herbzyme has been reported to alleviate ulcerative colitis by scavenging ROS, modulating the intestinal microenvironment, suppressing KIT proto-oncogene, receptor tyrosine kinase (KIT)/hypoxia-inducible factor 1-alpha (HIF-1α) and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) inflammatory signaling (Figure 1), and restoring epithelial barrier integrity[15]. Whether phosphatase-like activity directly contributes to KIT signaling regulation remains unclear. Future studies should therefore distinguish the anti-inflammatory effects of herbal compounds such as berberine from those attributable to nanoassembly-dependent catalytic function.

A practical experimental strategy would be to separate purified herbzyme nanoparticles from residual soluble small-molecule fractions. Parallel intervention groups could then be used to compare their independent and combined biological effects and to clarify the contribution of catalytic regulation.

Translational challenges and future perspectives of herbzyme

Therapeutic design and targeted delivery of herbzyme

The translational value of herbzyme should be assessed in relation to its intrinsic catalytic properties rather than by treating it simply as another nanocarrier. Phosphatase-like activity, for example, has been linked to inhibition of kinase-related signaling in *Rhizoma Polygonati* and may provide a basis for combination strategies with kinase inhibitors[16]. However, future directions should determine whether herbzyme activity can be retained, controlled, and spatially delivered.

Tissue specificity is a major challenge as catalysis is difficult to control, but biomimetic surface engineering, pH-, ROS-, or light-responsive intelligent modulation can be applied to control herbzyme to be active in pathological sites[17–19].

Standardization, biosafety, and scalable manufacturing

For translation, herbzyme must be defined and manufactured reproducibly. Quality control should include yield, particle-size distribution, standardized enzyme activity units, and batch-to-batch reproducibility. Established nanozyme assay frameworks provide a useful reference, but herbzyme-specific standard materials and guidelines should be established[8]. Biosafety evaluation including biocompatibility, pharmacokinetics, biodistribution, clearance, off-target effects, and dose–response relationships should also be performed. Omics studies of effects on DNA or proteins are also warranted to assess safety[20]. These data are necessary before therapeutics can move toward clinical evaluation. Conventional thermal Paozhi or prolonged boiling may produce variability in particle yield and catalytic activity, which is a manufacturing concern that requires herbzyme-specific validation. The central manufacturing objective is to achieve reproducible production of a compositionally and catalytically defined material.

Advanced structural characterization and mechanistic elucidation

Mechanistic clarification requires moving beyond morphological observation toward direct characterization of catalytic structure. Atomic force microscopy (AFM) has provided evidence of nanoscale assemblies, but the three-dimensional geometry of catalytic sites remains unresolved. Cryogenic electron microscopy, high-resolution spectroscopy, and complementary structural methods may identify substrate-binding regions in sufficiently ordered herbzyme assemblies. Integrating structural data with *Km*/*Vmax* measurements and chemical perturbation experiments would provide a more rigorous basis for defining structure-activity relationships.

Quantum-mechanical calculations have been used to model possible phosphatase-like reactions in herbzyme-related assemblies[1]. However, quantum tunneling has not been investigated in herbzyme catalysis. Future

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studies should therefore explore this mechanistic hypothesis with an explanatory model supported by evidence.

AI-assisted discovery and rational design of herbzyme

AI may become a powerful tool once sufficiently standardized herbzyme datasets are available, which should include integrated Paozhi parameters, particle morphology, structure, surface groups, chemical composition, catalytic kinetics, and enzyme types and activities. Such datasets could support prediction of catalytic subtypes, processing-structure-activity relationships, and design novel herbzymes.

Current AI systems for protein-structure prediction or *de novo* enzyme design cannot be directly transferred to heterogeneous, non-protein-based herbal nanoassemblies. AlphaFold and emerging enzyme design frameworks therefore provide methodological inspiration rather than validated tools for herbzyme design[11–12]. Herbzyme-specific AI models should be developed alongside prospective experimental validation.

Smart formulations and emerging applications

Stimulus-responsive formulations may offer an efficient approach for smart herbzyme development. Carbon-dot nanozyme studies have shown that pH- or light-dependent catalytic switching can regulate antibacterial or antioxidant activity, providing proof-of-concept strategies that may be tested in herbzyme systems[18]. Responsive hydrogels or microneedle-based local delivery could also reduce systemic exposure and be further developed for use in acupuncture (Figure 1), though these applications remain prospective. Thus, future application studies should prioritize formulations that address a defined translational direction, such as local retention, controlled activation, or reduced off-target exposure.

Concluding perspectives

Herbzyme is a novel concept for processing-derived catalytic assemblies that may connect traditional Paozhi with modern nanocatalysis. Herbzyme distinguishes itself not only in enzyme-like activity but also in the coexistence of catalytic nanoassemblies with retained herbal phytochemicals, which needs to be clarified by each contribution or intersection. The future direction of the field should therefore focus on a number of questions: What constitutes a herbzyme? Which components form its catalytic sites? How do processing conditions determine assembly and catalytic function? What proportion of the biological effect is attributable to nanoassembly-dependent catalysis rather than retained phytochemicals? Addressing these questions will be more informative for designing and exploring novel types of enzyme-like activities.

For translation, standardized characterization, catalytic assays, batch reproducibility, storage stability, biosafety assessment, pharmacokinetic evaluation, and scalable manufacturing are also in high demand. Advanced structural characterization and data-driven screening may subsequently shift herbzyme research from empirical discovery toward mechanism-guided design.

AI-assisted screening, responsive formulations, and other emerging technologies may broaden future studies. Quantum effects remain a hypothesis requiring direct experimental support. A mature herbzyme field will ultimately require a scientific framework that is conceptually defined, mechanistically interpretable, quantitatively measurable, reproducibly manufacturable, and translationally assessable.

Conflict of interest statement

Yingqiu Xie is an editorial board member of *Acupuncture and Herbal Medicine*.

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Author contributions

Yingqiu Xie contributed to conceptualization, funding acquisition, resources, writing, and editing.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

Not applicable.

Declaration of generative AI in scientific writing

AI-assisted tools were used for literature organization, language editing, and preliminary figure development. The author reviewed, verified, and edited the scientific content and remains responsible for the final manuscript.

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