Advancements in herbal medicine-based nanozymes for biomedical applications

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Abstract
Nanozymes are a distinct category of nanomaterials that exhibit catalytic properties resembling those of enzymes such as peroxidase (POD), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Nanozymes derived from Chinese herbal medicines exhibit the catalytic functions of their enzyme mimics, while retaining the specific medicinal properties of the herb (termed "herbzymes"). These nanozymes can be categorized into three main groups based on their method of synthesis: herb carbon dot nanozymes, polyphenol–metal nanozymes, and herb extract nanozymes. The reported catalytic activities of herbzymes include POD, SOD, CAT, and GPx. This review presents an overview of the catalytic activities and potential applications of nanozymes, introduces the novel concept of herbzymes, provides a comprehensive review of their classification and synthesis, and discusses recent advances in their biomedical applications. Furthermore, we also discuss the significance of research into herbzymes, including the primary challenges faced and future development directions.
Keywords: Herbzymes; Nanozymes; Traditional Chinese medicine; Carbon dots; Polyphenol–metal; Herbal medicine

Introduction

Herbzymes refer to nanozymes with varying enzymatic activities and derived from Chinese herbs through methods such as processing, chelation, and self-assembly [Supplementary Figure 1, http://links.lww.com/CM9/C405]. Since the 2007 study by Gao *et al*[1] discovered that ferroferric oxide nanoparticles (NPs) have peroxidase (POD) enzyme activity, more than 1000 different types of nanozymes have been reported. These encompass a wide range of materials, including metal oxides, noble metals, and carbon materials, as well as metal-organic framework materials and metal single-atom-carbon-doped materials.[2] With the increasingly prevalent concept of green chemistry and the nation's high regard for the development of traditional Chinese medicine (TCM), research into nanozymes based on Chinese herbs has gradually come into focus.

In 2015, Youyou Tu won the Nobel Prize in Physiology or Medicine for her groundbreaking discovery of artemisinin and dihydroartemisinin. These compounds are found in *Artemisia annua* and are effective in combating malaria.[3] This accolade highlighted the significance of TCM and prompted a notable increase in research efforts. However, TCM faces challenges such as poor efficacy, slow onset, low solubility of the active ingredients, low bioavailability, short half-life, instability in biological environments, and unclear mechanisms of action.[4] These limitations severely hinder the development and application of TCM. Since Chinese scholars first proposed the concept of nanomedicine in 2000, innovative research that combines Chinese medicine with nanomedicine has been pushed onto the world stage.[5] Nanotechnology applications such as the nano-formulation of active ingredients, whole herb nano-sizing, and nano-formulation of complex prescriptions fall under the umbrella of nanomedicine in TCM.[6] Interdisciplinary research addresses shortcomings in the practical application of Chinese medicine, thus allowing deeper exploration of the potential medical value of Chinese medicine. This approach has contributed significantly to the modernization of TCM at the international level.

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Nanomedicines synthesized from Chinese herbs include herb carbon dots (CDs),[7] complexes formed by natural polyphenols and metal ions,[8] and NPs formed through self-assembly of herbs.[9] These possess the distinctive pharmacological properties inherent in Chinese herbs, and also exhibit enzyme-like catalytic activities typical of nanozymes (e.g., POD-like, superoxide dismutase [SOD]-like, catalase [CAT]-like, etc.). Nanozymes from herbs have found diverse applications in medical therapy, bio-imaging, food science, ion detection, and environmental monitoring through leverage of both their herbal medicinal benefits and nanozyme functionalities. Despite numerous reports on the application of nanotechnology to traditional herbs, a comprehensive review that focuses specifically on nanozymes from herbs has yet to be undertaken. Therefore, in this article we introduce the term "herbzymes" to classify nanozymes sourced from herbs, while providing a comprehensive overview of their synthesis techniques, classification, enzyme-mimicking catalytic properties, and diverse applications. In addition, we discuss the intrinsic pharmacological activities and mechanisms of action of herbzymes with the aim of expanding and advancing their clinical applications. Finally, we emphasize the significance of research on herbzymes, and address the current problems and challenges associated with their application.

Nanozymes

Concept and basic properties of nanozymes

Nanozymes are a group of enzyme mimics that exhibit the distinctive characteristics and catalytic functions of nanomaterials.[10] Fe_3O_4 NPs with POD-like activity were first reported in 2007 by Gao *et al*[1]. These authors later coined the term "nanozyme" in 2013, spurring further research in this field. Nanozymes exhibit superior performance compared to natural enzymes, traditional enzyme mimics, and common nanomaterials, including high activity, stability, ease of modification, the ability to tune activity, multifunctionality, and cost-effectiveness in scaling up.[11] They also have unique optical, electrical, magnetic, and acoustic properties, enabling applications in disease diagnosis and treatment,[12] biosensing,[13] environmental monitoring,[14] and food safety.[15] Nanozymes were selected by the International Union of Pure and Applied Chemistry as one of the top 10 emerging technologies in chemistry in 2022.

Endogenous anti-oxidant system maintains redox homeostasis and fights oxidative damage. It involves natural enzymes including SOD, CAT, and glutathione peroxidase (GPx), as well as small molecules such as glutathione (GSH).[16] However, most natural enzymes are protein-based, giving rise to inherent limitations such as susceptibility to denaturation, complex purification procedures, and challenges in storage and reuse. In contrast, nanozymes have better physicochemical stability, versatility, and recyclability.

Classification of nanozymes based on their catalytic activity

Nanozymes possess catalytic activities similar to various natural enzymes, such as POD, SOD, CAT, GPx, oxidases (OXD), glucose OXD, proteases, esterases, and nucleases. Their activity is affected by nanomaterial composition, size, shape and surface modifications, as well as by external conditions such as pH, ionic strength, light, and temperature.[10] As a result, nanozymes can exhibit varying catalytic capabilities, or even multiple enzyme activities simultaneously. Each of these activities can synergistically contribute to a cascade reaction system, enabling autonomous generation of intermediate products and forming a closed-loop reaction. This ability significantly enhances the reaction efficiency. In recent years, rapid advances have occurred in the field of nanozymes, including notable progress in the quantification of their catalytic activities. Several methods for measuring nanozyme catalytic activity have been endorsed by national standards, enabling quantification of the enzyme-like behavior of nanozymes. The adoption of standardized methods allows rigorous assessment of nanozyme-related products, thereby improving the reproducibility and precision of nanozyme analytical techniques.[10] The following section briefly introduces typical enzymatic activities to illustrate the methods and applications used to measure nanozyme activity.

POD-like nanozymes

The natural oxidoreductase POD enzyme, consisting of diverse proteins/RNA, catalyzes substrate-peroxide reactions with hydrogen peroxide (H_2O_2) as an electron acceptor and is widely used in many industries.[17] The catalytic activity of POD nanozymes in the presence of H_2O_2 is commonly evaluated by colorimetric assays with various POD substrates, such as 3,3′,5,5′-tetramethylbenzidine (TMB), 4,4′-bi-2,6-xylidine (DAB), o-phenylenediamine (OPD), and 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS). This assessment includes determining the initial reaction rate (V0), the specific enzyme activity (SA) per unit, as well as calculation of the Michaelis constant (Km) and catalytic rate constant (Kc) based on the relationship between substrate concentration and reaction rate.[18]

Fe_3O_4 nanozymes are some of the earliest classic POD-like nanozymes to be discovered. Their activity and characteristics have been enhanced through surface modifications and complexation with metal ions. Fe_3O_4 nanozymes have been extensively applied in various fields, such as tumor diagnosis and therapy. As the concept of nanozymes has become more commonplace, a wide range of nanomaterials have been found to possess POD-like enzymatic activities.

SOD-like nanozymes

SOD is a class of metalloenzymes that plays a crucial role in catalyzing the conversion of superoxide anion ($O_2^{\cdot-}$) into molecular O_2 and H_2O_2. This enzymatic activity is essential for maintaining redox homeostasis and combating oxidative stress within biological systems. Natural SODs are classified into four types based on their cofactors: copper–zinc SODs, manganese SODs, iron SODs, and nickel SODs.[19] Artificial SOD nanozymes mimic natural SODs in scavenging $O_2^{\cdot-}$. However, their better stability, cost-effectiveness, and adjustable catalytic activity means they can potentially be used to treat oxidative stress-related diseases.[20] *In vitro* techniques for evaluating SOD nanozymes encompass a variety of methods, including assays for xanthine and xanthine oxidase, riboflavin photoirradiation, dihydroethidium, nitroblue tetrazolium (NBT), iodonitrotetrazolium chloride (INT), water-soluble tetrazolium salt (WST-8), and cytochrome C, as well as electron spin resonance (ESR) spectroscopy.[21] By employing a combination of these assays, the occurrence of false positives and false negatives in the evaluation of SOD-like activity in nanozymes can be reduced.

Carboxyfullerenes were the first reported materials with SOD-like enzymatic activity.[22] Advances in nanotechnology and materials science has led to the development of approximately 100 types of SOD nanozymes, most of which are composed of transition metals and C, N, O and S. Mechanistic studies and widely applied nanozymes include ceria-based,[23,24] carbon-based[25] and metal-based[26] nanozymes. Zhang *et al*[27–29] designed a series of CD nanozymes with exceptionally high SOD-like activity. These were effective at scavenging reactive oxygen species (ROS) and alleviating oxidative stress in a mouse stroke model and in an inflammatory bowel disease (IBD) model.

CAT-like nanozymes

CAT catalyzes H_2O_2 breakdown to O_2 and H_2O, thereby reducing cellular H_2O_2, acting as an anti-oxidant, and maintaining redox balance. In contrast to endogenous CAT enzymes, synthetic CAT nanozymes present benefits including low cost, size-dependent properties, high efficiency, and good stability, leading to their extensive utilization in diverse disciplines.[30] CAT-like nanozyme activity can be assessed by mixing with H_2O_2 and observing the formation of bubbles. Quantification is carried out by monitoring the dissolved O_2 and H_2O_2 absorbance at 240 nm. Furthermore, the reaction of terephthalic acid (TA) with H_2O_2 generates a fluorescence emission peak at 420 nm that can be used to confirm the CAT activity of nanozymes via the reduction in fluorescence.[31,32] Nanomaterials with CAT enzyme activity include metals, metal oxides, metal organic framework (MOF), carbon-based nanomaterials, metal sulfides, and Prussian blue.[30] The catalytic mechanisms of CAT can be classified into homogeneous and inhomogeneous cleavage according to the breaking of H–O or O–O bonds of H_2O_2. These CAT-like nanozymes can act as anti-oxidants by converting endogenous H_2O_2 to O_2. This is beneficial for alleviating hypoxia in tumors or inflammation, and for meeting the O_2 needs of photodynamic therapy (PDT), sonodynamic therapy, and radiotherapy.

GPx-like nanozymes

GPx is an essential selenium-containing protein enzyme involved in anti-oxidant defense mechanisms in the body. It mainly reduces H_2O_2 to H_2O with GSH, and can also reduce lipid peroxides to their corresponding alcohols, thus protecting cells from oxidative damage. Various nanomaterials mimic the activity of GPx and can be used for H_2O_2 removal, cell protection, and disease treatment. The main detection method for GPx-like nanozyme activity is the nicotinamide adenine dinucleotide phosphate (NADPH) technique, whereby GPx catalyzes the reaction between H_2O_2 and reduced GSH, thereby oxidizing the GSH and reducing NADPH to $NADP^+$.

Research on nanomaterials with only GPx-like enzymatic activity is still in its infancy. Wu *et al*[33] developed MIL-47(V)-X (MIL stands for Materials of Institute Lavoisier; X = F, Br, NH2 , CH3 , OH, and H) nanozymes with GPx-like activity by altering MOF ligands. The *in vivo* experiments showed that MIL-47(V)-NH_2 and MIL-47(V)-F (MVF) were effective in treating certain diseases. Zhang *et al*[34,35] reported a Janus liposozyme formed by co-assembly of seleno-phospholipid liposome-based nanozyme (SeL) and 2-([5′-(4-[diphenylamino] phenyl)-(2,2′-bithiophen)-5-yl] methylene)malononitrile (TDTM) for the treatment of diabetic foot ulcers. These findings indicate that high-performance GPx-like nanozymes can be used independently for biomedical therapy. Moreover, structure-activity studies are helpful in the design of *in vivo* therapeutics by offering a new nanozyme design and biomimetic study strategy.

OXD-like nanozymes

OXD enzymes in peroxisomes use O_2 as the electron acceptor in redox reactions to oxidize substrates and reduce O_2 to H_2O_2. These enzymes are integral to the metabolic processes of substances and energy in aerobic organisms, and have diverse applications in several industries. Many inorganic nanomaterials have OXD-like nanozyme activity that use O_2 to oxidize substrates, producing color and H_2O/H_2O_2. Amino-containing substrates such as TMB, OPD, and ABTS are used to assess oxidase-like activity, as their oxidized forms cause visible color and ultraviolet (UV)-visible signal changes.[36]

Cascade nanozymes

Cascade reactions, also referred to as tandem reactions, involve the integration of a minimum of two reactions within a single operation. In biological systems, multi-enzyme cascade reactions operate seamlessly without intermediate separation, effectively confining the collaborating enzymes within compartments to optimize catalytic efficiency. However, natural enzyme utilization is limited by high cost, strict requirements, and low stability. Rapid advances have recently been made in cascade reaction systems catalyzed by at least one nanozyme. Biomimetic cascade catalytic systems that use nanozymes usually progress sequentially, with output from one enzyme serving as input for the next. Such systems are widely used in biosensing, disease treatment, and anti-oxidant therapies.[37] The construction of nanozyme cascade reaction systems includes two main approaches: integration of nanozymes with natural enzymes (through physical adsorption, covalent bonding, and *in situ* encapsulation), and the fabrication of nanozymes that possess multiple enzymatic functionalities. This strategy makes it possible to create robust and efficient catalytic systems able to perform complex biochemical transformations, thus overcoming certain limitations of natural enzymes.[38]

In this section, we summarized nanozyme types, properties, and components to help understand their differences and to direct future research. Because of their unique nanomaterial and enzymatic features, nanozymes have become a research focus and hold great potential. In the future, nanozymes are expected to solve complex problems. As research on nanozymes progresses, scientists are using the perspective of biocatalysis to study drugs and nanomaterials. This helps to understand the *in vivo* catalytic behavior and nanomedicine action of nanozymes, thus opening new avenues for innovation in biomedical and other fields.

Herbzymes and Their Application

Rapid advances have recently been made in the field of nanozymes. However, the primary composite materials are predominantly inorganic, which are limited by long production times, toxicity, and poor sustainability. Over the past several years, a new class of nanozyme based on organic materials (organic nanozymes) has been introduced. Their versatility and wide application are important for sustainable development in agriculture, food, and the environment.[39] Among them, a subset of nano-TCM synthesized from herbs has been found to exhibit enzyme-like catalytic activities. We therefore introduce the concept of "herbzymes", which refers to nanozymes derived from TCM. These are processed through various methods such as preparation, chelation, or self-assembly to create different enzymatic activities. Figure 1 summarizes the classification, synthesis methods, and applications of herbzymes.

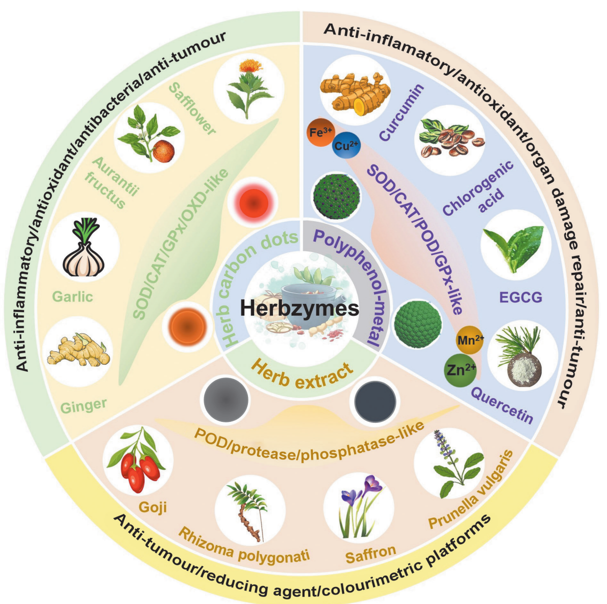

Figure 1: Herbzymes and their application. Herbzymes include herb carbon dot nanozymes, polyphenol-metal nanozymes, and herb extract nanozymes. These exhibit different nanozyme characteristics and have different applications. CAT: Catalase; EGCG: Epigallocatechin gallate; GPx: Glutathione peroxidase; OXD: Oxidases; POD: Peroxidase; SOD: Superoxide dismutase.

Overview of TCM

TCM encompasses herbal, animal-based, and mineral medicine. In recent years, the Chinese government has issued several successive policy documents such as the "Implementation Plan for Major Projects for the Revival and Development of Traditional Chinese Medicine (2023)" to actively promote development and innovation in the TCM industry.

Numerous attempts have been made to elucidate the material basis of TCM. The pharmacological effects are determined by its active components. However, many of the active components in TCM face limitations such as uncontrollable quality, poor solubility, poor stability, low bioavailability, short half-life, instability in the biological environment, and lack of targeting. All of these factors can impede the production and use of TCM for high-quality drugs.[40]

Nanotechnology has accelerated progress in TCM, broadened its application, and enhanced its therapeutic efficacy in disease management and prevention.[41,42] It can improve solubility, stability, permeability, pharmacokinetics, bioavailability, and circulation time. Moreover, nanotechnology can help to improve the effects of TCM by promoting sustained release, better targeting, reduced dosage, overcoming resistance, and enabling multi-component delivery.[43] Prof. Bihui Xu[44] introduced the notion of nano-TCM, defined as active ingredients, active components, raw materials, and compound drugs with a diameter less than 100 nm and produced through nanotechnology. Nano-TCM represents an advance in the preparation of Chinese herbs rather than a novel pharmaceutical entity. The most widely studied nano-TCMs to date are mainly nano-delivery systems derived from Chinese herbs, including nano-structures,[42] nano-vesicles,[45] and self-assembled nano-particles.[6] These have greatly expanded the development of TCM in various fields.

Herbzyme classification

As nanotechnology and detection methods continue to mature, researchers have found that many nano-TCMs exhibit enzymatic activities similar to those of natural enzymes such as POD-like, SOD-like, CAT-like, and GPx-like. When coupled with the active components of TCMs, this confers each type of nano-TCM with unique therapeutic effects. Nano-TCMs have found widespread application in areas such as tumor treatment, inflammatory diseases, organ and tissue damage repair, cardiovascular diseases, metabolic diseases, and imaging.

Three main types of herbzymes have been reported: herb CD nanozymes, polyphenol-metal nanozymes, and herb extract nanozymes. The verified enzymatic activities mainly include POD-like, SOD-like, CAT-like, and phosphatase-like hydrolase activities. These are widely used in inflammatory diseases, oxidative stress, organ damage, and anti-bacterial applications. A summary of the classification, synthesis methods, and application of herbzymes is presented below.

Herb CD nanozymes

CDs are advanced nanomaterials with a size of 2–10 nm and considered as zero-dimensional carbonaceous materials. Their conjugated Sp^2 domain and surface functional groups possess diverse optical and pharmacological properties.[46] CDs are categorized as graphene quantum dots, carbon quantum dots, carbon nanodots, and carbonized polymer dots. They have been widely used in fluorescent labeling, bioimaging, drug delivery, disease treatment, and biosensing. The widespread use of CDs is attributed to their remarkable photoluminescence properties, photostability, water solubility, biocompatibility, ease of chemical modification, and low toxicity. Furthermore, the exceptional catalytic properties and environmental compatibility of CD nanozymes has recently attracted significant research activity and funding.[47]

As the concept of green chemistry gains widespread acceptance, CDs derived from various sustainable sources including vegetables, fruits, food, and beverages are being researched and applied.[48] TCMs have attracted widespread attention because of their extensive application in various intractable diseases, including the anti-malarial drug artemisinin, the mineral drug arsenic trioxide for treatment of acute promyelocytic leukemia, and Lianhua Qingwen for combating the Severe Acute Respiratory Syndromes (SARS) and Corona Virus Disease 2019 (COVID-19) viruses. However, most TCMs have complex, large structures and poor water solubility, thus hindering their absorption and full function in humans. Therefore, researchers have begun to prepare various nanoscale drugs derived from TCM, of which CDs extracted from TCM have been found to possess multiple biological activities.[49]

The practice of using charred TCM for hemostasis dates back to the Song Dynasty in China, as documented in "Shi Yao Shen Shu" from almost 900 years ago. There are 27 types of charred medicines listed in the 2020 "Chinese Pharmacopoeia". According to TCM theory, the charring or burning of TCM alters some properties such as qi and flavors. However, the main effects or specific medicinal aspects of TCM remain unchanged. This is known as "preserving nature" and is the basis for charred drug application. Today, charred TCM is being explored as TCM carbon dots (TCM-CDs). Since the first reported use of ginger CDs for cell intervention and disease treatment by Li *et al*[50]. In 2014, research on TCM-CDs has increased rapidly. TCM is inherently rich in sugars, acids, phenolic compounds and glycosides. These dehydrate at high temperatures to form furfural molecules, which then polymerize to form aromatic clusters, and finally carbonize to form carbon cores.[49] Therefore, different TCMs have different contents of active components. The biological activities of their derived CDs also vary and have been widely applied in biological imaging and disease treatment.

Polyphenol-metal nanozymes

Polyphenols occur widely in various plants such as curcumin, catechins, ellagic acid, quercetin, tannic acid, epigallocatechin gallate (EGCG), and resveratrol. They have multiple properties including anti-oxidant, radio-protective, anti-cancer, and anti-microbial activities, making them widely applicable in the fields of medicine, food, and cosmetics. Plant polyphenols often contain common chemical groups such as catechol and ortho-quinone groups that can interact non-covalently. They also form stable metal-polyphenol networks by binding with multiple transition metal ions, endowing them with strong adhesion. However, their inherently poor water solubility and low bioavailability limits their clinical application. The combination of plant polyphenols with nanotechnologies via interaction with metal ions greatly broadens their application and has attracted significant interest from researchers.

In recent decades, polyphenol-metal nanomaterials have had major impacts in biomedical fields such as biosensing, drug delivery, bioimaging, and anti-tumor and anti-microbial therapy. The ease of synthesis, tunable structures, and good biocompatibility of these nanomaterials makes them ideal for disease diagnosis and treatment. They can also be used to build effective biosensing platforms for the detection of biomolecules such as proteins and nucleic acids, thus also facilitating early diagnosis and treatment. The discovery of nanozyme properties of polyphenol-metal nanomaterials further enhances our understanding of their mechanism of action and expands their application in inflammatory diseases and anti-oxidant therapies. Directions for future research in this area include the discovery of more polyphenol-metal nanomaterials with diverse nanozyme properties, standardization of the synthesis process and detection methods, and their possible application in various industries.

Herb extract nanozymes

Advances in nanobiology, nanomedicine, supramolecular chemistry, and various electron microscopy and imaging techniques have deepened our understanding of the molecular basis of TCM. Many herbs were found to form natural nanostructures during decoction, providing a good explanation for their therapeutic mechanisms. Nanosizing of herbs leads to significant changes in their biological and physical properties. Research has shown that some nanosized herbs exhibit hydrolytic and redox enzyme-like activities, thereby enhancing the therapeutic efficacy of the herb. However, further research is needed to investigate whether these NPs exhibit other types of enzyme activity.

Although there are numerous NPs in TCM extracts, few researchers have explored their enzyme-like activities. Major factors that affect the nanozyme activities of Chinese herbal extracts are firstly the type of TCM. Different Chinese herbal extracts contain different enzyme-like activities, which may be related to the pharmacological properties of the herbal medicine itself. Secondly, different synthesis methods for Chinese herbal extracts may affect the enzyme-like activities of NPs in the extracts. Changes in time, temperature, and reagent parameters for the same method could also affect the enzyme-like activities of NPs in the extracts. Finally, nanozyme determination methods and standards may also affect the apparent enzyme-like activity. Currently, only POD enzyme-like nanozymes have unified determination standards and methods, and the enzyme-like activities of other nanozymes may vary according to the standards and methods used. A better understanding of the enzyme-like activities of NPs in Chinese herbal extracts should help to identify the active sites of TCM and the mechanism of action, allowing further development and application in various fields.

Synthetic methods for herbzymes

Herbzymes are mainly divided into three types: herb CD nanozymes, polyphenol-metal nanozymes, and herb extract nanozymes. Each type has different synthesis methods. Herb CD nanozymes are mainly synthesized through top-down and bottom-up approaches. Polyphenol-metal nanozymes are synthesized by a simple one-pot method, while the commonly used synthesis methods for herb extract nanozymes include boiling, roasting, mechanical grinding, high-pressure microfluidics, and microwave techniques. These diverse methods allow herbzymes with specific properties to be made according to the different requirements and application scenarios. The development and optimization of different synthesis methods is critical to improving the quality, activity, and stability of herbzymes, while simultaneously promoting their application in various fields.

Herb CD nanozymes

The synthesis of CDs typically involves two main approaches: the "top-down" and "bottom-up" methods. The former entails disintegration of larger molecular carbon substances into smaller carbon NPs via chemical or physical means. Conversely, the "bottom-up" approach involves the aggregation of small molecular carbon materials into larger carbon NPs through specific chemical processes, typically involving the pyrolysis or carbonization of small organic molecules. "Top-down" synthesis requires strict conditions such as the use of concentrated acids and arc discharge, thus limiting its application.[51] Both synthesis methods can be used to synthesize high-quality CDs.

Currently, "bottom-up" approaches include hydrothermal, pyrolysis, solvo-thermal, and microwave-assisted methods. The most commonly used technique for the preparation of TCM-CDs is the hydrothermal method, as it does not require additional substances for passivation and modification, thereby maximizing biocompatibility and reducing toxicity. This method has been successfully applied to a variety of natural Chinese medicinal materials.[52] The same type of TCM can be synthesized on CDs with different properties by using different methods. For example, Li *et al*[50] obtained CDs with blue fluorescence from ginger juice by treatment at 300°C for 2 h with the hydrothermal method. However, Isnaeni *et al*[53] synthesized CDs with brown fluorescence from ginger using the microwave method for 5–40 min. Li *et al*[54] used ginkgo fruit to prepare nitrogen-doped CDs (N-CDs) by microwave-assisted and hydrothermal methods. N-CDs synthesized by the hydrothermal method were found to have smaller particle size, higher fluorescence intensity, and better fluorescence emission properties. The formation process for TCM-CDs involves multiple carbonization reactions that are largely uncontrollable, leading to synthesized TCM-CDs with a variety of properties. Therefore, understanding the mechanism of CDs is fundamental to the study of CD nanotechnology.

The conversion of TCM into CDs generates by-products that must be removed by purification methods such as centrifugation, precipitation, membrane filtration, electrophoresis, and dialysis. Subsequently, the TCM-CDs are characterized by their photoluminescent properties, morphological characteristics, elemental composition, and hybrid forms.[55] Common characterization techniques include transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), X-ray diffraction (XRD), Ultraviolet-Visible (UV-Vis) absorption spectroscopy, Fourier-transform infrared spectroscopy (FT-IR), and fluorescence spectroscopy (FL). In summary, a comprehensive understanding of the characteristics of TCM-CDs is instrumental in elucidating the relationship between the structure and performance of various TCMs, thereby paving the way for novel applications and enhanced performance of these traditional materials.

Polyphenol-metal nanozymes

The abundant phenolic hydroxyl groups in polyphenols can coordinate with different metal ions to form NPs, mesoporous structures, capsules, or coatings. Natural polyphenol-metal NPs are typically prepared using a simple one-pot method, where metal ions and polyphenolic compounds react directly in a solution. They can spontaneously undergo coordination assembly without the need for special solvents or external sources of heating, electricity, or light, making the preparation process simple and environmentally friendly. Mesoporous and capsule-shaped polyphenol-metal NPs are usually prepared using template methods, where sacrificial templates are incorporated during synthesis and subsequently removed to obtain MOFs with multi-level pore structures. Common templates include silica microspheres, calcium carbonate particles and emulsion droplets, while ethanol, hydrofluoric acid, and ethylenediaminetetraacetic acid can be used as clearing agents. Thin films and coatings of polyphenol-metal nanomaterials can impart special properties and functions to substrates, enabling functional modification. Methods such as deposition, spray coating, and electrochemical assembly are often employed for their preparation.[56]

Herb extract nanozymes

There are numerous types of TCMs with diverse properties, and different TCMs require distinct processing methods. According to the World Health Organization, processing methods for TCMs include boiling, steaming, roasting, stir-frying, and baking. These are mostly aimed at neutralizing toxicity, reducing side effects, and enhancing therapeutic effects. Nanotechnology for TCM preparation encompasses direct nanonization of TCMs, or the use of nanocarriers to carry herbs. Methods for direct nanonization typically include boiling, calcination, mechanical grinding, high-pressure microfluidics, and microwave technology. Nanocarrier technology refers to the use of nanomaterials to carry drugs, including nanoliposomes, solid lipid NPs, nanomicelles, and nanocrystals.[57–59] The synthesis methods for nanozymes derived directly from TCMs mainly include decoction, calcination, and mechanical grinding. The enzyme-like properties are then detected in NPs obtained directly from TCM extracts.

Application of herbzymes

Herbzymes have shown many promising applications in different fields, bringing new hope for breakthroughs and opening new possibilities for the treatment of multiple diseases. Herbzymes integrate the pharmaceutical properties of Chinese herbal medicines with the special properties of nanozymes, thus enabling novel capabilities in fields such as anti-inflammation, anti-tumor, anti-bacteria and anti-oxidation treatments, as well as organ damage repair and biosensing.

Herb CD nanozymes

Recent research has revealed that TCM-CDs have both the intrinsic fluorescent properties of CDs and enzymatic-like activities. They can mimic the catalytic activities of natural antioxidant systems such as POD, SOD, and CAT, demonstrating a high capacity for scavenging ROS and reactive nitrogen species (RNS). TCM-CDs have been extensively utilized in the treatment of oxidative stress and inflammation-related diseases. As mentioned previously, methods for assessing the nanozyme activities of TCM-CDs typically involve the use of TMB, ABTS, and NBT to determine the ability to clear free radicals and $O_2^{·-}$, which is indicative of their anti-oxidant enzymatic activity. However, it should be noted that many TCM-CDs with anti-oxidant functions have yet to be systematically or specifically validated for their POD, SOD, and CAT enzymatic activities. Instead, their anti-inflammatory and ROS-clearing capabilities have simply been verified, with these TCM-CDs being classified as herbzymes. Inflammatory diseases are characterized by excessive activation of the immune system, resulting in abnormal secretion of cellular inflammatory factors and ROS. This subsequently amplifies the inflammatory response and causes more damage, such as IBD and stress-induced gastric ulcers. In recent years, various TCM-CDs have been developed with free-radical scavenging abilities and excellent therapeutic effects on inflammatory diseases. These include gallic acid,[60] rhein,[61] atractylodes macrocephala,[62] Radix Sophorae Flavescentis carbonisata,[63] safflower/*Angelica* sinensis,[64] *Aurantii fructus* immaturus,[65] genistein,[66] Honeyberry[67] and garlic[68] [Table 1].

Gallic acid is a polyphenolic compound widely present in plants such as Rheum palmatum and possessing multiple biological activities, including anti-inflammation, anti-oxidation, and anti-viral properties. To expand its application, Liu *et al*[60] synthesized gallic acid-CDs from polyethyleneimine (PEI) and gallic acid, and modified its surface with PEG_{2000}. Total *in vitro* anti-oxidant capacity was determined using ABTS and 2,2-Diphenyl-1-picrylhydrazyl (DPPH), SOD enzyme activity using WST-8 and ESR, GPx enzyme activity using 5,5′-Dithiobis-(2-nitrobenzoic acid) (DTNB), and CAT enzyme activity using the direct oxygen production method. The results showed that CDs had multiple nanozyme activities similar to SOD, GPx, and CAT, could simulate the intracellular anti-oxidant defense system, showed selective accumulation in the kidneys, significantly inhibited ferroptosis, and could be used to treat acute kidney injury. Rhein is a bioactive component isolated from Rheum officinale, Cassia tora, and Polygonum multiflorum. It can inhibit the release of pro-inflammatory factors, but has limited application due to poor solubility and toxicity. Xia *et al*[61] synthesized rhein CDs (RA-CDs) using the hydrothermal method with doped L-arginine rhein. The ABTS, DPPH, NBT and TMB methods showed that RA-CDs had strong ROS scavenging and anti-oxidation abilities. RA-CDs were also shown to have SOD-like enzyme activity, with good imaging results and therapeutic effects in animal models for both prevention and delayed treatment of ulcerative colitis. Gastric ulcers are a common clinical gastrointestinal condition related to increased oxidative stress and inflammation. Kang *et al*[62] synthesized a series of CDs from seven kinds of charred herbs using the hydrothermal method. CDs synthesized from *Atractylodes macrocephala* (SCNDs-1) were found to inhibit 90% of stress-induced gastric ulcers by reducing the expression of inflammatory factors and alleviating an excessive neuroendocrine response. Hu *et al*[63] used Radix Sophorae Flavescentis carbonisata (RSFC) to synthesized RSFC-CDs by one-step pyrolysis. In a gastric ulcer model, the RSFC-CDs pretreatment group showed increased levels of anti-oxidant enzymes (CAT, SOD, GSH-Px) and anti-oxidant GSH, decreased levels of the lipid peroxidation products malondialdehyde and inducible Nitric Oxide Synthase, and balanced levels of anti-oxidants and peroxidation in the body.

In addition to the treatment of inflammatory diseases, the nanozyme activity of TCM-CDs can also be used in other anti-oxidant applications, such as food preservation. Using a hydrothermal method, Kuang *et al*[69] synthesized CDs derived from *Salvia miltiorrhiza* (SmCDs) and showed they could delay the senescence of post-harvest, flowering Chinese cabbage. Compared to the control group, cabbage treated with SmCDs effectively inhibited chlorophyll degradation and significantly cleared accumulated ROS after harvest. Treatment with SmCDs significantly enhanced the activities of POD, SOD, CAT and other anti-oxidant enzymes on the 7th, 14th, and 21st days of storage. This reduced membrane lipid peroxidation and maintained a dynamic balance in ROS metabolism, thereby mitigating ROS-induced damage to plants and delaying the senescence of harvested cabbage.

Other TCM-CDs possess OXD-like and GPx-like activities, allowing the conversion of O_2 to $O_2^{·-}$ for application in anti-bacterial and anti-tumor diseases. Chang Huan Tsung and Zhu Tong synthesized CDs derived from fresh ginger and dried ginger, respectively, using hydrothermal and microwave-assisted hydrothermal methods. CDs from fresh ginger had OXD-like activity and could

Table 1: Synthesis methods, nanozyme activities, and applications of different herbs carbon dots herbzyms.

Herbs	Synthesis method	Nanozyme activities	Mechanism of action	Application
Gallic acid	Hydrothermal	SOD/CAT/GPx	Scavenging ·OH, $O_2^{\cdot-}$ H_2O_2, ROH, ABTS	Acute kidney injury[60]
Rhein	Hydrothermal	SOD	Scavenging ABTS, DPPH, ·OH, $O_2^{\cdot-}$	Ulcerative colitis[61]
Atractylodes macrocephala	Hydrothermal	Non-measured	Reduction of inflammatory factors and oxidative stress	Stress-induced gastric ulcers[62]
RSFC	Pyrolysis	Non-measured	Anti-inflammatory and anti-oxidative effects	Acute gastric ulcer[63]
Safflower and *Angelica sinensis*	Hydrothermal	Non-measured	Inhibited the expression of inflammatory cytokines	Rheumatoid arthritis[64]
Aurantii fructus immaturus	High-temperature roasting	Non-measured	Inhibiting xanthine oxidase activity	Antihyperuricemic and anti-gouty arthritis[65]
Genistein	Solvothermal	Non-measured	Scavenging DPPH, ROS, and RNS	Antioxidant and anti-inflammatory *in vitro*[66]
Honeyberry	Hydrothermal	Non-measured	Decreased DPPH and ABTS levels; increased the expression of antioxidant enzyme; reduced proinflammatory markers and upregulated anti-inflammatory markers	Anti-inflammatory, antioxidant, and neuroprotection *in vitro*[67]
Garlic	Hydrothermal	Non-measured	Scavenging DPPH, ·OH	Cellular imaging and antioxidant[68]
Salvia miltiorrhiza	Hydrothermal	Non-measured	Scavenging H_2O_2, $O_2^{\cdot-}$	delaying senescence of postharvest flowering Chinese cabbage[69]
Ginger	Hydrothermal and microwave-assisted	Non-measured	Producing ROS; reduced the expression of pro-inflammatory factors	Anti-tumor healing[50]; accelerates wound[50,70]
Coffee	Hydrothermal	GSH oxidase/OXD	Induce ferroptosis and increase H_2O_2, ·OH	Anti-tumor[71]
Turmeric	Hydrothermal	Non-measured	Scavenging DPPH, ABTS, and producing ROS	Antibacterial and antioxidant[72]

ABTS: 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulfonic acid); CAT: Catalase; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; GPx: Glutathione peroxidase; GSH: Glutathione; OXD: Oxidases; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; RSFC: Radix sophorae flavescentis carbonisata; SOD: Superoxide dismutase.

generate a large amount of intracellular $O_2^{\cdot-}$, which significantly inhibited the growth of subcutaneous tumors in an animal model.[50] CDs derived from dried ginger had good anti-inflammatory activity *in vivo* and *in vitro*, and significantly reduced expression of the pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and NO, thus promoting rapid healing of rat skin wounds.[70] Yao *et al*[71] reported on a type of CD prepared from chlorogenic acid (ChA-CQDs), the main bioactive natural product in coffee. These authors found that ChA-CQDs exhibited clear GSH-like activity and could promote the ferroptosis of cancer cells by interfering with a lipid repair system catalyzed by GPX4. ChA-CQDs could also significantly inhibit *in vivo* tumor growth in HepG2 tumor-bearing mice. In mice carrying the H22 liver cancer cell line, ChA-CQDs recruited a large number of tumor-infiltrating immune cells, including T cells, NK cells, and macrophages. This resulted in the conversion of "cold" tumors to "hot" tumors through activation of the systemic anti-tumor immune response.

Polyphenol-metal nanozymes

Some nanomaterials formed by polyphenols and metal ions have been shown to possess enzyme-like properties. Curcumin, an ancient natural anti-inflammatory drug extracted from the rhizomes of turmeric, consists of two adjacent methoxyphenols and a β-diketone group. The diketone part can bind to metal ions and form metal chelates, which have been extensively studied. Curcumin can form nano-complexes with some metal ions that exhibit nanozyme activity. In 2005, Barik *et al*[73] reported that the curcumin–copper nano-complex exhibited SOD nanozyme activity. A curcumin–copper nano-complex was formed through coordination between one copper atom, one acetate group, and one H_2O molecule with the enol-keto groups of curcumin. The SOD activity, free radical neutralization capacity, and anti-oxidant ability of this nano-complex were demonstrated using NBT and DPPH methods, indicating it could serve as a new SOD mimetic. Subsequently, Zhang *et al*[74] and another group[75,76] reported that a curcumin-iron complex exhibited both SOD and CAT nanozyme activities. This complex could effectively clear excess ROS at disease sites and reduce inflammatory markers, thus displaying anti-inflammatory and anti-oxidant effects.

Rosmarinic acid (RosA) is a polyphenolic compound isolated from the rosemary plant. It exhibits significant anti-oxidant, anti-inflammatory, anti-microbial, and anti-cancer effects. However, its poor solubility, low permeability, photo-instability, and rapid metabolism limit its clinical application. Self-assembly of RosA, or coordination with metal ions into NPs, improves its solubility and imparts nanozyme properties. Chung *et al*[77] utilized polyethylene glycol (PEG)-modified RosA to self-assemble into RosA NPs (RANP). These had the ability to remove H_2O_2 and protect cells from H_2O_2-induced damage. Yuan *et al*[78] generated RosA-Mn NPs with cascading SOD/CAT nanozyme activity and the ability to eliminate ROS and alleviate acute kidney injury. Chen *et al*[79] chelated RosA with Fe^{3+} to form Fe-RA NPs. These exhibited both POD-like enzyme activity and GSH depletion characteristics, thereby promoting iron-dependent cell death. Wen *et al*[80] constructed Danshensu B (SalB)-copper cluster nanozymes (SalB-CuNCs) with SOD/CAT cascading nanozyme activity. Loading SalB-CuNCs onto chitosan, chondroitin sulfate, and hydrogen peroxide enzyme-based hydrogels (COC@SalB-Cu hydrogel) further demonstrated that COC@SalB-Cu hydrogel efficiently promoted diabetic wound healing. Wang *et al*[81] prepared chlorogenic acid (ChA)-manganese chloride NPs (ChA-Mn NPs) with free-radical scavenging ability and SOD enzymatic activity. These NPs showed liver-targeting and anti-inflammatory properties in acute liver injury models. Zhang *et al*[82,83] synthesized a metal-polyphenol network/cerium oxide artificial nanozyme (MPN@CeOx) with EGCG and CeOx for ROS elimination and CT/MRI imaging. They also generated Cur-MPN wrapped in yeast cell walls (CM@YM) that had SOD activity, scavenged free radicals, and alleviated DSS-induced colitis while regulating the intestinal microbiome [Table 2].

Herb extract nanozymes

Nanozymes derived from Chinese herbal extracts possess many advantages, such as being non-toxic and environmentally friendly, while retaining herb characteristics. Benassi *et al*[86] and Kazybay *et al*[87] reported that a NP extract of Rhizoma polygonati and Goji could self-assemble into nanoflowers and exhibit hydrolytic enzyme properties that were protease-like, phosphatase-like and α-amyloid. These authors also used protein evolution analysis methods to predict and verify other enzymatic activities. For example, Rhizoma polygonati NPs had fructose-bisphosphate aldolase cleavage enzyme activity, and Goji NPs had POD enzyme activity.[88] Deer velvet extract has various functions, but its enzyme components and activities are largely unknown. Nazarbek *et al*[89] reported that deer velvet extract particles have POD and phosphatase activities and can be used in anti-cancer treatment. They also applied network pharmacology to verify the alkaline phosphatase activity of Honghua and Xihonghua extract particles, and subsequently investigated the underlying mechanism for their anti-COVID-19 effect.[90]

TCM is rich in flavonoids, alkaloids, and polyphenolic active compounds. These components provide a continuous green reducing agent for the synthesis of NPs, while endowing them with nanozyme properties. For example, the *Prunella vulgaris* (Pr) extract is rich in multiple active compounds. Marvi *et al*[91] used Pr as a natural reducing agent to directly reduce platinum ions to platinum NPs (PtNPs). PtNPs were characterized by various techniques including UV-Vis, TEM, zeta potential analysis, FT-IR, and energy dispersive spectroscopy. These methods confirmed that the Pr/PtNPs surface has many functional groups derived from

Table 2: Synthesis methods, nanozyme activities, and applications of different polyphenol-metal herbzyms.

Herbs	Metal ions	Synthesis method	Nanozyme activities	Mechanism of action	Application
Curcumin	Cu^{2+}	One-pot	SOD	Scavenging DPPH, $O_2^{\cdot-}$	Scavenging free radical *in vitro*[73]
Curcumin	Fe^{3+}	One-pot	GPx	Scavenging DPPH, ABTS, ·OH, H_2O_2	Acute kidney injury[74], cute lung injury[75], autoimmune uveitis[76]
Rosmarinic acid	Mn^{2+}	One-pot	SOD/CAT	Scavenging ABTS, DPPH, $O_2^{\cdot-}$, ·OH	Cute kidney injury[77]
Rosmarinic acid	Fe^{3+}	One-pot	POD	Producing·OH, and depleting the high GSH levels	Antimor[78]
Salvianolic acid B	Cu^{2+}	One-pot	SOD/CAT	Scavenging $O_2^{\cdot-}$, H_2O_2	Accelerating diabetic wound healing[79]
CA	Mn	One-pot	SOD	Scavenging ABTS, DPPH, $O_2^{\cdot-}$, ·OH; anti-inflammatory; restore autophagic function	Acute liver injury[80]
EGCG	Fe^{3+}	Template/one-pot	SOD	Scavenging $O_2^{\cdot-}$, ·OH, ABTS; anti-inflammatory	Ulcerative colitis[81,82]
Quercetin	Fe^{3+}	One-pot	Non-measured	Scavenging DPPH, ABTS, ·OH; avoid cell apoptosis	Rheumatoid arthritis[84]
Tannic acid	Fe^{3+}	Template	POD/CAT	Scavenging H_2O_2, and producing ·OH; promoting ferroptosis death	Antimor[85]

ABTS: 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulfonic acid); CA: Chlorogenic acid; CAT: Catalase; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; EGCG: Epigallocatechin gallate; GPx: Glutathione peroxidase; GSH: Glutathione; POD: Peroxidase; SOD: Superoxide dismutase.

herbal extracts. The authors also demonstrated using TMB and DPPH methods that Pr/PtNPs have POD nanozyme activity and anti-oxidant effects. Moreover, they developed a colorimetric platform that uses POD nanozyme activity to achieve highly selective quantification of glutamate levels. This can be widely applied in biomedicine, food science, and environmental monitoring.

In summary, herbzymes represent a significant advance in the field of nanozymes and a major innovation in the study of TCM. Because of the intricate components and varied pharmacological effects, TCM has long been a subject of interest. However, the practical applications of TCM have been hindered by several challenges including low efficacy, delayed onset, and limited stability. Integration with nanotechnology has revitalized the use of TCM by improving its effectiveness and the availability of herb treatments.

Due to their nanostructure, herbzymes exhibit both the pharmacological properties of TCM and enhanced catalytic activity. This novel integration of TCM with modern nanotechnology is a promising direction for the advancement and globalization of TCM. Moreover, research on herbzymes has fostered interdisciplinary collaboration and progress, and facilitated the utilization of nanotechnology in diverse sectors including healthcare, food science, and environmental protection. We conducted a systematic review of the current synthesis methods, classification, and various application scenarios of herbzymes. This deeper understanding should lead to more effective use of the abundant resources of TCM for the development of innovative solutions to address various health and environmental challenges in contemporary society.

Challenges and Perspectives

To accelerate the development and application of herbzymes in various fields, we have summarized the opportunities and challenges for the future from our perspective.

Preparation of herbzymes

The activity of herbzymes varies with the source of TCM, and the same TCM can yield enzymes with different activities depending on the synthesis method. Given the multi-component nature of most TCMs, the preparation of herbzymes requires selection of the effective components and removal of excess impurities and non-essential elements. It is important to optimize the physicochemical properties of herbzymes during synthesis to ensure pharmacological activity, high enzymatic activity, physical stability, and longevity of the enzymatic activity. Therefore, it is imperative to identify the optimal processing methods that control the enzymatic and pharmacological activities of herbzymes.

Deciphering the catalytic sites and mechanisms of herbzymes

Current research on herbzymes is predominantly focused on the measurement and application of catalytic activity and types, with little attention paid to identification of the catalytic sites and elucidation of the mechanisms of herbzyme action. This is essential from both theoretical and experimental perspectives, including study of the structural changes that occur between the herbzymes and substrates during the catalytic process. Advanced molecular or atomic-level techniques can also be employed to delineate the entire catalytic process of herbzymes. Unlike conventional nanozymes, the catalytic activity of herbzymes may be influenced by the type of TCM and the doping of reductants, as well as other elements. The nanostructure and catalytic activity of TCM may also be affected after processing, self-assembly, or chelation with other metal ions. These studies are of great significance for the future synthesis of more effective herbzymes.

Expanding the catalysis types and application fields of herbzymes

Current research on herbzymes is mainly limited to simple redox reactions, which is primarily relevant to biomedical fields such as anti-inflammation, anti-oxidation, and anti-bacterial treatments. Less investigation has been carried out on the hydrolase and isomerase activities of herbzymes and their applications. Future research directions for herbzymes include strengthening the redox reactions, enhancing catalytic activity, and the exploration of non-redox reactions, as well as the development of applications in industries such as chemical engineering, energy, food preservation, and environmental protection.

Toxicity of herbzymes

The metabolism and distribution of nanomaterials has long been a controversial topic. Although herbzymes are inherently eco-friendly catalysts, there is limited research on their metabolism and distribution, and their potential impact on the human body is not well understood. Further investigations are needed into the metabolic pathways, distribution, and chronic toxicity associated with long-term treatment of different herbzymes. Additional studies are also required on their biocompatibility for sustainable and scalable clinical applications and commercialization.

Establishment of a database for herbzymes

The current literature and data on the classification and catalytic types of herbzymes is still limited. As the number of published studies increases, it will be necessary to establish a database for herbzymes based on existing TCM databases. Integration with TCM databases will allow analysis of the mechanisms and structure-activity relationships of herbzymes, while laying the foundation for a theoretical system of herbzymes.

Conclusions

TCM has played a vital role in the treatment of various diseases as a complementary or alternative medicine, but the material basis for TCM activity has yet to be studied in depth. Nanomedicine has become a favored tool for TCM research, and has expanded the development and application of TCM. The discovery of nanozyme activity in TCM presents a novel strategy to investigate the material properties of TCM and expand the realm of nanozyme research and applications. Consequently, we introduce the concept of "herbzymes" to categorize nanomaterials with nanozyme activity that are derived from herbs. This proposal establishes a standardized nomenclature for nano-TCM, enhances the research focus in this field, and encourages further investigations that should ultimately advance the position of TCM on the global stage.

In conclusion, herbzymes represent a novel avenue for investigating TCM and nano-TCM. Despite still being in the early stages, research on herbzymes is progressing rapidly. This approach allows the mechanism of action of TCM in various diseases to be studied through the lenses of biocatalysis and nanozymes, as well as elucidating the active components from the perspective of nanozymes. Future advances in herbzyme technology will bring fresh vitality to the development and application of TCM.

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Conflicts of interest

None.

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