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Nanozyme-armed probiotics: Mastering redox modulation for synergistic therapy

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ABSTRACT

Probiotics encompass a diverse assortment of biological activities and are widely distributed in barrier organs, which enables them to dynamically modulate multiple physiological processes within the human body. Due to their diminished side effects, a spectrum of probiotic-centric functional formulations has been used as an alternative to traditional anti-inflammatory drugs. Nonetheless, probiotics are intrinsically sensitive to environmental fluctuations, which greatly limits their therapeutic effectiveness. The specific combination of probiotics with nanozymes opens up novel perspectives for resolving this issue. Nanozymes are nanomaterials that exhibit enzyme-like properties, showcasing exceptional catalytic prowess while retaining the distinctive attributes of nanomaterials. The alliance of nanozymes and probiotics demonstrates a significant synergistic effect in the treatment of diseases. On one hand, inherent targeting and metabolic properties of probiotics impart nanozymes with site-selectivity, alongside the capacity to fine-tune the catalytic microenvironment for optimized activity. On the other hand, nanozymes exhibit exceptional catalytic properties that can be leveraged to safeguard probiotics and concurrently bestow new bioactivities, thereby enhancing their therapeutic efficacy. This review underscores the therapeutic potential of nanozyme-enhanced probiotics in regulating reactive oxygen species for the synergetic therapy of various diseases, as well as the challenges associated with the biosafety of such biomimetic functional agents.

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1. Introduction

Probiotics are defined as "live microorganisms that provide health benefits to the host when consumed in adequate amounts" [1]. They possess a variety of surface molecules that facilitate interaction with their environment, thereby manifesting a plethora of biological characteristics, such as motility, specific surface adhesion, hypoxic propensity [2]. Through these abundant features, probiotics bestow numerous health benefits on the host organism [3]. From the perspective of ecosystem, the interaction between crops and weeds mirrors the competitive dynamics between probiotics and pathogens, each striving for dominance in their ecological niches. Under pathological conditions, the harmonious balance between the host system and the microbial community is disrupted, leading to the occurrence of diseases [4]. By introducing probiotics to regulate the microbiota, "dysbiosis" can be converted into "synergistic homeostasis". Harnessing the interplay between the microbiome and the host can refine the microenvironment within troubled spots, thereby amplifying the therapeutic impact (Fig. 1).

Through the nuanced regulation of microbiota interaction, probiotics fulfill diverse functions, such as the competitive displacement of pathogens, the augmentation of the intestinal barrier, the modulation of the host's immune system, and the facilitation of neurotransmitter synthesis [5]. Due to their robust biological activity and wide-ranging roles, probiotics are well-suited for therapeutic applications [6,7]. Notably, substantial progress has been made in the clinical translation of bacterial-related therapies. Several probiotic-related therapies have already received approval from the U.S. Food and Drug Administration (FDA). For example, the *Bacillus Calmette–Guérin* (*BCG*) vaccine was approved in 1990 for the

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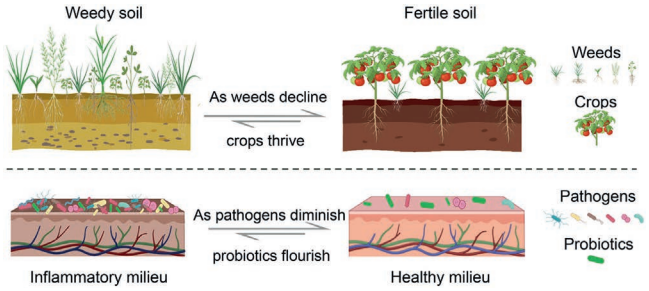


Fig. 1. Schematic representation illustrating the analogy between soil-weed-crop and milieu-pathogen-probiotic. From an ecological standpoint, the interaction between the host and its microbiota parallels the interdependence of soil and vegetation. Vegetation encompasses both weed and crop, while the microorganism comprises pathogen and probiotic. The type and condition of the soil dictate the type and distribution of vegetation, and conversely, the diversity of plants in turn acts on the soil to influence its biodiversity. This ecological interplay is akin to the dynamic balance maintained between the host's internal environment and its microbial inhabitants.

treatment of bladder cancer [8]. In 2023, the FDA further approved fecal microbiota transplantation (FMT) for the treatment of recurrent *Clostridium* difficile infection [9]. These approvals mark significant progress in the clinical translation and regulatory acceptance of probiotic-based therapies. Detailed examples of probiotic-based clinical applications and the corresponding regulatory progress are summarized in Section S1 (Supporting information).

Nonetheless, one of the main challenges in their application is that probiotics are highly susceptible to interference from environmental factors, which might reduce colonization capacity of probiotics and further decrease their bioavailability [10–12]. In respect to the naturally moderate therapeutic efficacy of probiotic, several strategies have now been crafted to tackle these issues [13]. Biomineralization is frequently employed for crafting protective shields around probiotics against the harsh conditions of the digestive tract, including gastric acid, bile salts, and digestive enzymes [14]. While typical cellular encapsulation holds promise for amplifying the beneficial effects of microorganisms, this approach can hinder the exchange of materials and information. Such limitations can substantially curb the proliferation and physiological activities of these microbes, rendering them in a state akin to hibernation [15]. Moreover, genetic engineering offers the potential to boost therapeutic effectiveness and reduce toxic side effects by precisely manipulating target genes. It can adjust the expression of various protein in bacteria, and thereby influence their inherent structure, function, behavior, or properties. However, the broader application of genetic engineering is still constrained by its complexity, the lag in trait expression, and long-term biosafety [16,17]. Although these aforementioned techniques can confer different exogenous functions to bacteria, they also come with certain limitations. Therefore, there is an urgent need to develop technologies that are user-friendly, therapeutically effective, and biologically secure, aimed at safeguarding probiotics and equipping them with innovative capabilities. In this regard, the emergence and advancement of nanozymes offer feasible avenues and diverse alternatives for obtaining engineered bacteria and achieving optimized therapies.

Nanozymes, nanoscale materials with enzyme-like catalytic properties, are characterized by their varied compositions, crystal structures, and surface morphologies [18]. In contrast to natural enzymes, nanozymes boast a range of substantial benefits: They are cost-effective and amenable to scalable production; the superior stability renders them ideal for long-term storage and transportation; their expansive surface area facilitates straightforward surface customization. These distinctive features have catapulted nanozymes to the cutting edge of various biomedical fields, captivating the scientific community in recent years [19,20]. Commercial nanozyme-based products have emerged in the field of high-sensitivity detection. A prominent example is the "magnetic nanozyme strip assays" invented by Yan's team, which has been effectively applied in detecting fecal occult blood and transferrin [21]. Abundant nanozymes are currently being engineered and utilized to manage the redox intracellular redox states, serving as supplements or substitutes for native oxidoreductases, including peroxidase (POD), oxidase (OXD), catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD) [22,23]. Through precise modulation of either "pro-oxidation" or "anti-oxidation" effects, nanozyme-based therapies can be tailored to distinct disease contexts. For example, in cancer treatment, OXD and POD activities can be exploited to deplete intracellular glutathione (GSH) and generate hydroxyl radicals (·OH), thereby inducing ferroptosis [24,25]. It can also synergize with photothermal therapy to enhance chemodynamic therapy (CDT) effects, achieving a multimodal synergistic antitumor effect [26]. In contrast, for oxidative stress-related diseases such as acute kidney injury, nanozymes mimic SOD and CAT activities to eliminate excess reactive oxygen species (ROS) and provide protective effects. These versatile mechanisms highlight the broad therapeutic potential of nanozymes in diverse pathological conditions [27,28].

Researchers have endeavored to integrate probiotics with nanozymes, thereby pioneering a novel category of site-specific therapeutic platforms (Fig. S1 in Supporting information). The integration of nanozymes with probiotics can lead to a synergistic effect in disease management, where the combined impact exceeds the sum of their individual benefits, embodying the principle that $1+1$ is greater than 2. Nanozymes can upgrade the living environment of probiotics, and endow probiotics with new functions. Probiotics facilitate the precise targeting and accumulation of nanozymes, and their metabolic byproducts can serve as substrates for nanozyme reactions [29]. This review focuses on the strategic application of nanozyme-armed probiotics for the accurate and dynamic regulation of redox microenvironment. By harnessing the targeted navigation of probiotics and the potent catalytic abilities of nanozymes, these biohybrid micro-medicines are designed to selectively mitigate heightened ROS levels at the pathological sites, thereby rejuvenating redox balance. Furthermore, the nanozyme-augmented probiotics can specifically eradicate detrimental microorganisms and cancerous cells through targeted chemodynamic interventions. The review culminates with an exploration of the obstacles and promising prospects that nanozyme-fortified probiotics present in the realm of therapeutic applications, providing groundbreaking perspectives and a roadmap for their integration into clinical practice.

2. Independent action of probiotics and nanozymes for ROS regulation

ROS, a group of highly reactive oxygen-containing compounds, are renowned for their Janus-like character within biological systems [30,31]. At low concentrations, ROS serve as signaling molecules in physiological processes, contributing positively to cell proliferation and immune responses. Nevertheless, disruption of the redox homeostasis can result in cellular injury and apoptosis, which is associated with a spectrum of pathological conditions, including inflammatory diseases, neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes [32–34]. Taking the dual role of ROS in immune action as an example, an appropriate level of ROS can activate the T cell receptor, enhance T cell proliferation, and promote cytokine secretion. On the other hand, excessive accumulation of ROS can dampen T cell responses, leading to immunosuppression [35].

A plethora of pharmaceuticals have been developed to modulate oxidative stress, as exemplified by nonsteroidal anti-

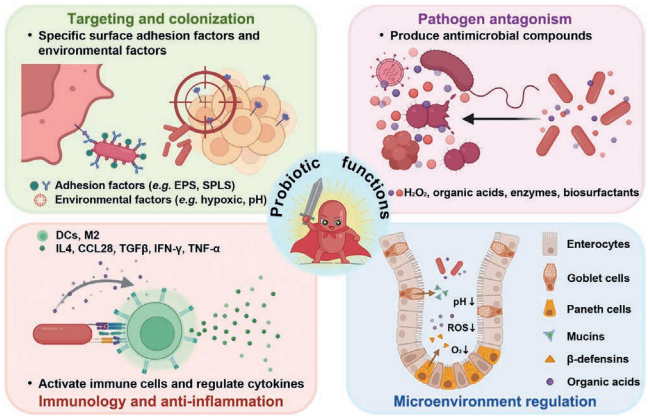


Fig. 2. The regulation of oxidative stress through the probiotics encompasses several mechanisms, including targeted colonization, pathogen antagonism, immunological modulation, anti-inflammatory effects, and microenvironment regulation.

inflammatory drugs (NSAIDs), which are extensively employed for their analgesic, antipyretic, and anti-inflammatory properties [36,37]. Nonetheless, the administration of NSAIDs is frequently associated with serious side effects, including gastrointestinal hemorrhaging, cardiovascular damage, and the worsening of asthma symptoms [38]. To tackle this unmet medical need, it is imperative to devise innovative therapeutic strategies that precisely target inflamed regions, elicit a localized anti-inflammatory immune response, and facilitate the restoration of the affected region's essential functions. Within this framework, researchers are investigating the potential of probiotics and nanozymes in modulating ROS levels, either by eliminating ROS to alleviate oxidative stress or by generating ROS for selective destruction of pathogens.

2.1. Probiotic intervention in oxidative stress management

Host-microbe interactions occur primarily at mucosal surfaces [39]. The ratio of the number of resident human bacteria to the number of human somatic cells is close to 1:1, and the sum of their microbial genomes far exceeds that of the human genome. Overall, the metabolic activity of the flora is equivalent to a virtual organ within the human body [40]. These microorganisms, as well as the proteins and metabolites they express, are constantly interacting with the human host and can directly or indirectly affect the host's redox balance [41]. As depicted in Fig. 2, probiotics play a pivotal role in numerous signaling pathways that aid cells in countering oxidative stress and mitigating inflammatory damage [42]. The detailed mechanisms of action are provided in Section S2 (Supporting information).

2.2. Nanozyme-mediated ROS generation and elimination

Due to their stable structures, plentiful active sites, and durable catalytic activity, nanozymes serve as reliable substitutes for natural enzymes and are extensively utilized in the regulation of redox dysregulation [43,44]. To date, numerous nanozymes have been engineered to mimic the functions of antioxidant enzymes effectively breaking down excessive superoxide anion ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) into more benign molecules like H_2O and O_2 (Fig. 3a) [45,46]. Additionally, POD-emulating nanozymes are commonly utilized to facilitate the conversion of H_2O_2 into highly reactive $^{\bullet}OH$, and OXD-resembling nanozymes can generate strongly oxidizing $O_2^{\bullet-}$ [47], crucial in the context of CDT (Fig. 3b) [48]. Beyond these intrinsic catalytic activities, nanozyme-based therapies are often integrated with other free-radical-associated treatments, encompassing photodynamic therapy (PDT), sonodynamic therapy

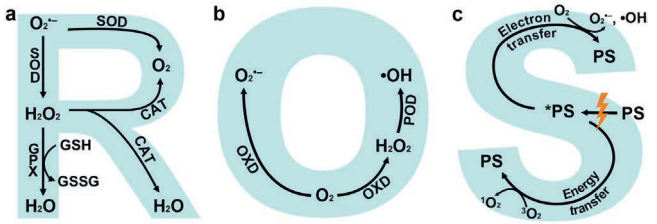


Fig. 3. Action mechanism of redox nanozymes. (a) Nanozymes replicate the antioxidative roles of SOD, CAT, and GPX to scavenge ROS. (b) Nanozymes imitate the prooxidant activities of OXD and POD to produce ROS. (c) The mechanisms of electron transfer and energy transfer involved in the generation of ROS by photo-excited PS.

(SDT), and radiotherapy (RT) [49–51]. In contrast to nanozymes, these nanocatalysts rely on external energy to produce ROS. To elucidate the unique mechanisms of ROS generation, PDT was used as an example to delineate its process. Upon activation, photosensitizers (PS) can generate elevated $O_2^{\bullet-}$ and $^1O_2$ through either electron transfer (pathway I) or energy transfer (pathway II) mechanisms (Fig. 3c) [52–54]. Representative examples are discussed in Section S3 (Supporting information).

3. Nanozyme-enhanced probiotics for restoring redox homeostasis

Probiotics and their distinctive components have the potential to treat disease by reducing inflammation, modulating immunity, balancing the microbiota, and enhancing barrier function [55]. But their efficacy is hampered by elevated levels of ROS in the pathologic microenvironment [56,57]. Given their high sensitivity to ROS, strictly anaerobic probiotics are prone to be damaged, thereby reducing their therapeutic impact and potentially extending the duration of treatment [58]. Nanozymes demonstrate ROS scavenging abilities that rival those of natural enzymes, featuring extensive activity against diverse toxic ROS and remarkable stability within the challenging conditions often present in disease contexts [59]. With these attributes, nanozymes can serve as a defensive "shield" for probiotics, potentiating the biotherapeutic impact on inflammatory conditions linked to an overabundance of ROS. These properties of nanozymes offer more possibilities for probiotic therapy and new options for overcoming stability limitations [60].

3.1. Combining nanozyme and bacterial components for anti-inflammation

Researchers have harnessed the active fractions of bacteria as an alternative to whole live bacteria, thereby preserving certain advantages of bacteria while circumventing the potential for bacterial infections caused by introducing the metabolic activity as well as the proliferative capacity of the bacteria [61,62]. An extensive range of bacterial components have been extensively developed, encompassing bacterial outer membrane vesicles, spores, and bacterial metabolites [63,64]. As a nanozyme carrier, it provides targeting function while performing biological functions such as immunomodulation. Detailed discussion on the combined use of nanozymes and bacterial derivatives for anti-inflammatory therapy is provided in Section S4 (Supporting information).

3.2. Harnessing nanozymes and probiotics to combat oxidative stress

However, harnessing the full therapeutic potential of probiotics solely through the use of non-viable bacterial components remains a challenge [65]. Preserving the integrity of the probiotic cell structure is essential for optimizing their metabolic activity and biological functions [66]. Consequently, there is a growing trend towards utilizing low-toxicity or attenuated bacteria, characterized

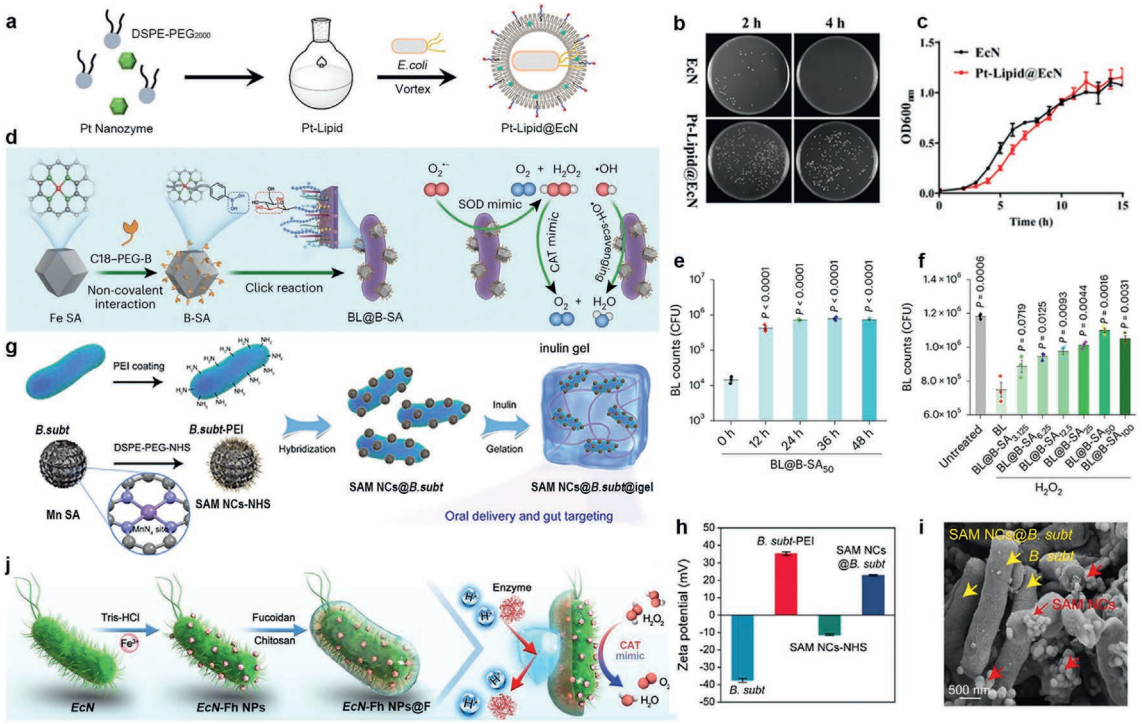


Fig. 4. Antioxidation therapy with nanozymes and probiotics. (a) Coating of *EcN* with a lipid-embedded Pt nanozyme layer. (b) Viability of coated *EcN* in pepsin-supplemented SGF. (c) Growth kinetics of *EcN* and Pt-Lipid@*EcN*. Reproduced with permission [70]. Copyright 2022, the Royal Society of Chemistry Group. (d) Fe SA attached to *BL* for the treatment of IBD. (e) Proliferation status of *BL*. (f) Survival rates of *BL*@B-SA and free *BL* after H_2O_2 exposure (200 μmol/L, 2 h). Reproduced with permission [72]. Copyright 2023, the Nature Publishing Group. (g) Inulin-coated SMA NCs@*B. subt* for colonic targeting and retention. (h) Zeta potential changes during the stepwise assembly process. (i) SEM image confirming the uniform and dense coating of nanozymes on the bacterial surface. Reproduced with permission [73]. Copyright 2024, the Elsevier. (j) One-step bio-mineralization for *in situ* growth of Fh NPs on *EcN*. Reproduced with permission [74]. Copyright 2024, the American Chemical Society.

by reduced lipopolysaccharide (LPS) or bacterial endotoxin levels, as therapeutic agents. These bacteria serve as platforms to introduce active probiotic metabolism and behaviors into the host, offering more effective and targeted treatments [67,68]. To bolster the survival and therapeutic efficacy of probiotics in harsh environments like gastric and intestinal juices, the application of bacterial surface coatings has been suggested [69]. These nanozyme-based multifunctional coatings serve a dual role: They act as a protective shield to maintain probiotic viability while also providing additional therapeutic advantages.

Ma *et al.* developed a coating, lipid-embedded platinum nanozymes, encapsulating *Escherichia coli* Nissle (*EcN*) 1917 for the treatment of ulcerative colitis (UC) (Fig. 4a) [70]. The platinum nanozyme-lipid coating successfully constructs a protective physical barrier on the surface of *EcN*, which not only effectively maintains the normal growth capacity of the probiotics but also significantly mitigates the damage caused by gastrointestinal stress on the bacterial cells. After 4 h of treatment in simulated gastric fluid (SGF), the lipid-coated *EcN* maintained high viability, whereas the uncoated free *EcN* was almost completely inactivated (Fig. 4b). Additionally, this coating exhibits ROS scavenging capability, which synergistically alleviates intestinal inflammatory responses and promotes the structural and functional recovery of the intestinal epithelial barrier. However, analysis of *EcN* growth behavior showed that coating resulted in a delayed growth period for encapsulated *EcN* compared to uncoated controls, which the researchers hypothesized could be due to the nanomaterial layer delaying the uptake of nutrients used for proliferation by *EcN* (Fig. 4c). Therefore, when selecting probiotic surface-functionalized nonenzymatic materials, it is necessary to consider several key factors, in addition to the protective effect on probiotics and the ability to effectively scavenge ROS, as well as the question of whether the surface-functionalized nanomaterials affect the growth behavior of the modified probiotic. This aspect is extremely important because any alteration in the growth kinetics of probiotics could potentially affect their therapeutic efficacy.

In order to better utilize the excellent catalytic activity of nanozyme, single-atom nanozyme (SAzyme) have come to the attention of scientists with their well-defined structures, maximum use of atoms, and excellent sustained catalytic activity [71]. In a study by Mao *et al.*, they ingeniously engineered *Bifidobacterium longum* (*BL*) armed with a SAzyme to treat inflammatory bowel disease (IBD) [72]. Fe SA binds to *BL* through a special linker molecule boronic acid-poly (ethylene glycol) (C18-PEG-B) (Fig. 4d). This approach enables rapid conjugation within 30 min. This innovative therapeutic strategy aims to enhance the probiotic's ability to fight the disease while maintaining its viability and functionality, and the linker molecule ensures that the probiotic's growth behavior is not impeded (Fig. 4e). Fe SA contains atomically dispersed active metal centers that effectively mimic natural SOD and CAT antioxidant enzymes to form an antioxidant defense system. Not only does this replace clinically used anti-inflammatory drugs, but it also protects the probiotic from the gastrointestinal tract and the disease environment. After 2 h of treatment under 200 μmol/L H_2O_2, the survival rate of the optimally modified probiotic group (with a B-Fe SA concentration of 50 μg/mL) was significantly higher than that of the unmodified group (Fig. 4f), indicating that the composite system effectively alleviates oxidative stress-induced damage to the probiotics. *BL* themselves have superior colonic colonization capacity, which in addition to their health effects on the host, ensures that the surface nanozymes provide sustained antioxidant therapy at the site of disease. In conclusion,

BL@B-SA synergistically reduced ROS levels to inhibit inflammation to restore the intestinal barrier and regulate microbiota homeostasis during treatment.

Based on the excellent catalytic activity of SAzyme, researchers have designed an advanced and complex probiotic treatment strategy that combines SAzyme, probiotics, and prebiotics. This strategy is characterized by its effectiveness, sustained targeting, retention, and high biocompatibility, meeting the comprehensive requirements of clinical needs for acute colitis. Wang *et al*. synthesized highly antioxidative single manganese atomic nanocatalyst (Mn SA) on *Bacillus subtilis* (*B. subtilis*) and further gelatinized them *in situ* using prebiotic carbohydrate-inulin (Fig. 4g) [73]. Initially, electrostatic interactions were employed to adsorb a layer of cationic polyethyleneimine (PEI) polymer onto the negatively charged probiotic surface, achieving preliminary assembly (zeta potential shifted from −38.5 mV to +36.4 mV). Subsequently, NHS ester groups exposed on the nanozymes underwent covalent reaction with amine groups of PEI, forming stable amide bonds for reinforcement (final zeta potential: +24.3 mV) (Fig. 4h). Scanning electron microscopy (SEM) imaging revealed uniform and dense coverage of nanozymes on the bacterial surface, demonstrating robust binding stability (Fig. 4i). The synthesized Mn SA possessed multiple catalytic antioxidant activities (SOD, GPX, and CAT) and these nanocatalysts were able to eliminate oxidative stress and *in vivo*. The *B. subtilis* used competitively consumes oxygen and inactivates harmful bacteria in dysfunctional colon. The use of inulin hydrogel wraps was used to improve colonic retention. SAM NCs@*B. subtilis* achieves high colonic targeting and sustained colonic retention by oral administration. Utilizing the synergistic antioxidant properties of Mn SA and modulation of gut microbiota, the designed probiotic gel significantly attenuated colitis in a mouse model.

In another groundbreaking study, Li *et al*. avoided a multi-step nanomaterial synthesis and anchoring process by growing biocatalytic ferrihydrite nanoparticles (Fh NPs) *in situ* on *EcN* through a one-step bioinduced mineralization process [74]. The resulting hydrotalcite nanostructures anchored on bacteria exhibited potent CAT-like activity over a wide pH range, effectively scavenging ROS to reduce inflammation, and further encapsulation of the fucoidan barrier endowed the probiotic with additional inflammatory colon-targeting functionality extending the therapeutic benefit of each therapeutic module (Fig. 4j). In addition to ROS scavenging, *EcN*-Fh NPs intestinal immunity by inhibiting neutrophil activity and repolarizing pro-inflammatory macrophages, providing a multi-pronged approach to treating IBD. This work explores simple yet effective strategies to seamlessly integrate nanocatalysts with probiotics and improve their targeting of inflammatory lesions to maximize the benefits of each therapeutic module. The powerful multifunctional probiotic platform further triggers enhanced therapeutic efficacy in targeting colitis through the synergistic action of nanocatalytic therapy, intestinal immunomodulation, and microbiota remodeling. Xu and his team developed a dual enzyme cascade system (*LGG*-M@P) for the treatment of IBD [75]. IMXene has catalytic properties to neutralize ROS in the gut and can be used as a vector to deliver the NLRP12 plasmid to activate the 12 genes NLR family pyrin structural domain to help suppress inflammation. Binding of M@P to *Lactobacillus rhamnosus GG* (*LGG*) *via* electrostatic adsorption synergistically inhibits inflammation and supports the restoration of intestinal flora through a cascade repair mechanism.

For synergistic enhancement, targeting strategies rely not only on the intrinsic tropism of probiotics but also on the functional modification of the nanozyme-armed probiotic surface, thereby markedly improving their targeting precision and mucosal retention capacity. Representative examples are provided in Section S5.1 (Supporting information). Beyond targeting optimization, recent studies have also expanded the therapeutic scope of nanozyme-probiotic systems to address broader pathological conditions. The combination of nanozyme and probiotic is not limited to the treatment of intestinal inflammation, but can be extended to the treatment of other diseases. In addition, this combination can also fully utilize other physiological functions of probiotics, such as their role in metabolic regulation (Section S5.2 in Supporting information).

4. Nanozyme-integrated probiotics to enhance chemodynamic therapy

Supraphysiological concentrations of ROS can inflict damage on a variety of macromolecules and perturb cellular functions, contributing to the onset and progression of various diseases [76]. At the same time, nanozyme-mediated CDT leverages the generation of highly reactive ROS to eliminate detrimental pathogens, notably bacteria and cancer cells [77,78]. The efficacy of POD-like nanozymes is influenced by several factors, including the pH levels, the concentration of H_2O_2, and the presence of GSH [79–81]. The integration of nanozymes with probiotics can elevate H_2O_2 levels and create an acidic milieu, thereby optimizing the local catalytic environment and augmenting the potency of CDT. Furthermore, probiotics facilitate tissue-specific targeting for nanozymes, not only enhancing the therapeutic efficacy but also reducing collateral damage to healthy cells [82].

Nanozyme can also be used as exogenous inducers as a switch for the probiotic metabolic factory achieving highly precise and predictable adjustable responses [83,84]. Chen *et al*. employed pH-dependent POD-like nanozyme (Fe Au) as inducible "promoter" and "effector" to modify engineered *Bifidobacterium longum* of the *BL*999 (*BL*) for switchable control of probiotics in cancer therapy [85]. Fe Au binds to *BL via* click chemistry between its own phenylboronic acid functional group and polysaccharides from the bacterial cell wall. Fe Au initially acts as an inducible "promoter" that generates trace amounts of non-lethal ROS stress to up-regulate the acidic metabolites in *BL*, short-chain fatty acids (SCFAs), acetic acid and lactic acid. Once the metabolites acidify the tumor microenvironment (TME) to a certain threshold, Fe Au is transformed into an "effector" that generates large amounts of lethal ROS to fight cancer. Due to the enforced anaerobic nature of *BL*, *BL*-Fe Au can specifically colonize tumors. Fe Au can selectively catalyze the conversion of H_2O_2 in acidic TME to highly cytotoxic ROS, while remaining harmless under physiological conditions. This environmental selectivity offers great potential as a tool to precisely regulate ROS levels, affecting the fate of bacteria and cancer cells in a specific manner. This strategy provides a new approach to modulate probiotic metabolism in pathological environments with therapeutic specificity and accuracy. The experimental use of individual nanozyme regulators that can act as both "promoters" and "effectors" and their adaptive switching between these roles in response to the pathological microenvironment enhances the maneuverability and relative accuracy of the system. Although effectors are designed to be activated in specific microenvironments, their stability and activity in complex biological environments may be influenced by pH, enzyme activity, and other biomolecules, which may affect their performance and controllability.

Immunotherapy is considered to be the most promising cancer treatment due to its long-lasting therapeutic activity and manageable side effects [86]. In parallel, CDT has recently been combined with immunotherapy to achieve synergistic antitumor effects, such as ferroptosis induction coupled with checkpoint blockade or metabolic regulation, which has become a current research hotspot [87–89]. Checkpoint blockade immunotherapy (CBI) is a widely applied strategy that employs monoclonal antibodies to block immunosuppressive pathways, thereby restoring T cell-mediated antitumor immune responses [90]. Reactivated $CD8^+$ T cells release interferon-gamma (IFNγ), which acts on tumor cells to downregulate SLC7A11 and SLC3A2 expression. This reduces

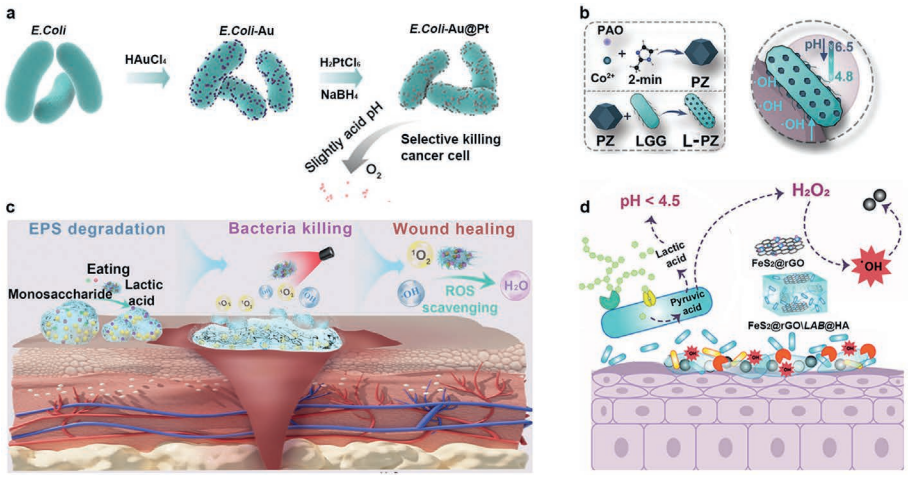


Fig. 5. Nanozymes collaborated with probiotics for CDT. (a) Cancer treatment utilizing *E. coli*-Au@Pt conjugates and CBI. Reproduced with permission [93]. Copyright 2021, the American Chemical Society. (b) Adaptive cancerous pyroptosis inducer composed of enzyme-like PZ and *LGG*. Reproduced with permission [95]. Copyright 2024, the John Wiley and Sons. (c) *LG* in conjunction with heterojunctions for biofilm countermeasures. Reproduced with permission [102]. Copyright 2024, the John Wiley and Sons. (d) Synergistic therapy of *Candida* vaginitis with FeS_2@rGO and *Lactobacillus*. Reproduced with permission [104]. Copyright 2023, the American Association for the Advancement of Science.

cystine uptake and depletes intracellular GSH, markedly weakening the antioxidant defense of tumor cells. As a result, tumor cells become more susceptible to T cell-mediated killing and ROS-based therapies [91]. It should also be noted that systemic administration of CBI may induce immune-related side effects in normal tissues, which requires careful management in clinical applications [92]. Han *et al*. designed a mild nanomedicine (*E. coli*-Au@Pt) in combination with CBI to achieve high anticancer efficacy even when used at low doses (Fig. 5a) [93]. Au@Pt nanozyme modified on the surface of *Escherichia coli* (*E. coli*) were used as nanomedicines to achieve precise CDT. The tumor-targeting ability of *E. coli* and the catalytic properties of Au@Pt under acidic conditions allowed the nanomedicines to efficiently release ROS in specific microenvironments. In addition, probiotic can stimulate the body to produce more than 68 % of T cells, and interferon gamma released by T cells specifically reduces the intracellular reductant GSH in tumor cells, while having no significant effect on normal cells [90,94]. As a result, ROS destroys only tumor cells and not normal cells, significantly increasing therapeutic efficacy and reducing side effects. This nanosystem achieves excellent combined CDT and CBI tumor therapy without increasing the dose of the nanomedicine itself, reducing the dependence of the nanomedicine on tumor targeting ability. It is noteworthy that ROS production is attributed to the catalytic conversion of dissolved oxygen on the *E. coli*-Au@Pt surface, but the low level of dissolved oxygen in the human environment may not be sufficient for CDT triggering conditions.

In addition, optimizing the catalytic microenvironment of nanozymes by membrane-adhered microbe enables potent cancer immunotherapy. Qu *et al*. designed an adaptive pyroptosis inducer (LPZ), consisting of an enzyme-like metal-organic framework as well as *LGG*, which was effective in inducing pyroptosis in cancer cells (Fig. 5b) [95]. Pyroptosis is a form of programmed cell death triggered by the activation of intracellular multiprotein complexes called inflammasomes. These inflammasomes can be activated by pathogen-associated molecular patterns such as LPS, imbalanced intracellular ion homeostasis, and excess ROS [96]. Among them, increasing ROS causing plasma membrane damage is considered to be an effective strategy to promote cellular pyrokinesis because it allows the rapid release of a large number of molecular patterns associated with danger [97]. In this study, polyamine oxidase (PAO) was incorporated into zeolitic imidazole framework-67 (ZIF-67) to form nanozyme with enzyme-like activity (PZ).The PZ utilize specific metabolites within the tumors as catalytic substrates for the production of H_2O_2 and $^{\bullet}OH$, which induce cellular pyrokinesis and reshape the tumor microenvironment to facilitate cancer immunotherapy [98]. However, the slightly acidic TME is not suitable for PZ to efficiently perform their catalytic and therapeutic functions. And ROS has the problem of short lifetime and limited diffusion distance [83]. In order to effectively compensate for the inherent problems of ROS and to achieve optimal membrane rupture efficacy, *LGG* was chosen to integrate with PZ to generate LPZ. *LGG* can produce organic acids through anaerobic respiration under anaerobic conditions, which helps to lower the pH of the intestinal lumen [99,100]. And the SpaC pilin of *LGG* can bind to mucin of host tissues, allowing *LGG* to settle on the surface of cancer cells. These unique features allow *LGG* to optimize the catalytic and therapeutic effects of nanozyme through its respiratory capacity and enhance anti-tumor immunity by enhancing the effect of ROS through its adhesion capacity [101]. When LPZ is used in combination with an immunostimulant (Indoleamine 2,3-dioxygenase, IDO), strong immune activation can be triggered. During treatment, *LGG* are eventually killed by ROS to stop their respiration preventing potential biosafety issues. In addition to optimizing the catalytic environment of nanozymes, the generation of catalytic substrates is also crucial for enhancing their therapeutic performance. Engineered or commensal bacteria can serve as endogenous sources of catalytic substrates, such as H_2O_2, thereby sustaining *in situ* catalytic reactions and improving treatment selectivity. Representative examples are provided in Section S6 (Supporting information).

CDT can be applied to flexible and dynamic bacterial therapy in addition to fixed tissue therapy such as cancer. Huang *et al*. combined *Lactobacillus rhamnosus* (*LG*) with heterojunctions (MXene (Ti_3C_2) quantum dots/FeS) to form probiotic bioheterojunction (*LG*-HJ), used to counteract biofilms (Fig. 5c) [102]. Extracellular polymeric substances (EPS) act as barriers during antibiotic therapy, restricting the penetration of antibiotics into biofilms and impeding their interaction with bacteria, resulting in suboptimal drug concentrations and antimicrobial ineffectiveness [103]. And the bacteria within the biofilm usually develop resistance, thus complicating biofilm removal. This innovation aims to break down sugars in the EPS to effectively combat biofilm-associated infections. *LG* uses sugars in the EPS of bacterial biofilms including

glucose, rhamnose, and maltose as raw materials for metabolism to produce lactic acid and effectively degrade the EPS within the biofilm to create favorable conditions for antimicrobial agents. Lactic acid was further catalyzed by lactate oxidase (LOx), integrated in the heterojunction, to produce H_2O_2, and FeS on the heterojunction surface further catalyzed H_2O_2 into $^{\bullet}OH$. Upon exposure to NIR light, heterojunctions triggered the PDT/PTT effect. This leads to the accumulation of large amounts of heat and ROS (including $^{\bullet}OH$ and $^1O_2$) in the wound, resulting in effective biofilm eradication. After anti-biofilm treatment, *LG*-HJ scavenges ROS and enhances the expression of CAT and SOD in cells, thereby protecting cells from ROS-induced damage and attenuating the nuclear factor-κB (NF-κB) inflammatory pathway, thereby accelerating wound healing. Wei *et al*. developed responsive hyaluronic acid (HA) hydrogel FeS_2@rGO/*Lactobacillus*@HA (FeLab) for the treatment of *Candida* vaginitis by combining POD-like FeS_2@rGO nanozymes with lactic acid and H_2O_2 produced by *Lactobacillus* spp. (Fig. 5d) [104]. FeLab exhibits both anti-*Candida albicans* and vaginal microbiota modulating activities. When applied to the vagina, hyaluronidase (HAase) secreted by *Candida albicans* and bacteria degrades HA, resulting in the local release of *Lactobacillus* and FeS_2@rGO nanozymes. Under enzymatic stimulation, the HAase responsive system achieved a release rate of *Lactobacillus* close to 100 % within 24 h, while almost no leakage occurred in the absence of HAase, demonstrating the pathogen triggered targeting capability of the system. On the one hand, *Lactobacillus* fermentation produces lactic acid, which normalizes the vaginal microenvironment and lowers the vaginal pH to 4–4.5. On the other hand, FeS_2@rGO nanozyme catalyzes the H_2O_2 produced by *Lactobacillus* to produce a large amount of $^{\bullet}OH$, which kills *Candida albicans* without affecting *Lactobacillus*. In *Candida* vaginitis mice, FeLab had significant anti-*Candida albicans* activity, but hardly damaged vaginal mucosal cells, which was favorable for vaginal mucosal repair. In addition, a higher proportion of thick-walled bacterial phylum (especially *Lactobacillus*) and a reduction of *Aspergillus* remodeled the healthy vaginal microbiota to reduce recurrence.

5. Conclusion and outlook

The combination of probiotic and nanozyme opens up an innovative strategy for specific disease treatment. This combined therapy leverages the biological characteristics of probiotics, such as targeting, adhesion, immunity, and metabolism, along with the catalytic properties of nanozymes that mimic enzymes, such as POD, SOD, CAT, and GPX (Fig. S4 in Supporting information). This integration achieves more precise targeting and dynamic therapeutic responses, thereby significantly enhancing treatment efficiency [105,106]. During treatment, this conjugate exhibit tunable catalytic activity and environmentally responsive properties. Not only is the protective effect on the probiotics greatly enhanced to ensure their stability and activity, but the excellent catalytic activity and efficiency of the nanozymes are also brought into full play, thus improving the overall therapeutic effect. The specific binding of probiotics and their components with nanozymes enables the controllable regulation of ROS in the lesion area. Over time, a variety of nanozyme-armed probiotic drugs have been developed to address a wide range of application issues, as detailed in Table S1 (Supporting information). This strategy makes the treatment site-selective and enables targeted treatment of the disease, improving the precision and effectiveness of the treatment. This work aims to elucidate the synergistic effects of probiotic and nanozyme, deepen our understanding of the therapeutic process, and lay an important scientific foundation for the development of more effective nanozyme-enhanced probiotic therapeutics. However, the development of nanozyme-armed probiotic is still in its infancy and faces numerous significant challenges and opportunities:

5.1. Defining the action mechanism of probiotic in disease treatment

Although studies have reported the biological activities of probiotics in disease treatment, the underlying molecular pathways are fragmented and exhibit strain specificity [107]. In the absence of mechanistic information, multiple trials and errors are required to determine the health benefits of microorganisms, which complicates the selection of indication-specific microbes and increases the difficulty of establishing clinical application guidelines for probiotics [108]. Clarifying the mechanisms of disease onset and the role of microorganisms within those mechanisms can align with the unique symbiotic relationship of the human-microbiome, enabling the development of targeted therapeutic approaches to better combat diseases.

Although the FDA's generally recognized as safe (GRAS) standard provides a basis for assessing the safe use of probiotics, there is still a lack of clear boundaries and mechanisms between pathogenic and probiotic to ensure the safety of the starter strains or probiotic strains. The biological characteristics of microorganisms are influenced by their adaptability to the environment. For instance, *Lactococcus lactis* (*L. lactis*) can enhance the host's immune capabilities, making it widely used in vaccine production [109]. However, in recent years, pathogenic *L. lactis* have been isolated from the blood and urine of patients suffering from endocarditis, which raises questions about the pathogenicity of *L. lactis*. Therefore, we need to systematically summarize the mechanisms of action of probiotics, classify them by strain specificity or pathway mechanisms, to help researchers analyze microbial activity and make rational choices of probiotics.

The uniformity in nutrient supply and metabolic pathways of homogeneous bacterial populations makes them unstable and vulnerable in complex environments, which restricts their productivity [110,111]. In contrast, multi-species bacterial consortia, by organically linking different metabolic pathways, disperse metabolic burdens, achieve cascade reactions, and transfer products, providing an alternative to single bacteria [17,112]. For example, consortia composed of autotrophic and heterotrophic bacteria can efficiently convert light energy into biomass energy or chemical energy to produce target products. However, maintaining the stability between different strains and maintaining reproducible colony ratios is currently a challenge, which seriously hinders the full release of the therapeutic potential of artificial consortia.

5.2. Constructing biosafe nanozymes with high activity and selectivity

Exploring the interaction mechanisms between nanozymes and probiotics, as well as optimizing methods for system construction, are crucial for enhancing their application effectiveness. Most research on nanozymes to date has primarily focused on improving their catalytic activity [113]. Thanks to the efforts of researchers, the enzymatic activity of some nanozymes has already surpassed that of natural enzymes [114,115]. Nevertheless, the performance of nanozymes in terms of catalytic specificity and substrate selectivity has not yet received adequate attention [116]. Combining nanozymes with molecular imprinting to create binding sites can achieve precise recognition and binding of target substances, thereby improving the selectivity and efficiency of the reaction [117].

The biosafety challenges of nanozymes in biomedical applications mainly arise from their potential toxicity in multiple organs such as the lungs, nerves, endocrine system, and immune system, as well as complex *in vivo* behaviors including protein corona formation, dynamic transformation, and cross-barrier transport. These mechanisms can cause long term damage *via* oxidative stress, inflammatory activation, and epigenetic modulation. Importantly, the toxicity of nanozymes is closely related to their physicochemical

properties, such as size, surface charge, and shape, and can be worsened by environmental factors. As a result, conventional toxicological models like cell-based assays, animal models, or organoid systems are insufficient for comprehensive risk assessment. Specific concerns related to nanozymes involve significant accumulation in organs, especially the liver, spleen, and lungs, after systemic administration. This is commonly observed in inorganic formulations such as those derived from Pt, Au, CeO_2, and graphene. Such prolonged retention increases the risk of chronic inflammation and organ dysfunction, highlighting the need for repeated dose and chronic toxicity studies beyond acute exposure tests. Degradation and clearance rates vary widely among materials. While some metal-origin nanozymes are slowly removed through macrophage uptake or hepatobiliary routes, designed biodegradable or renal clearable versions exhibit more efficient excretion. Nevertheless, the potential toxicity and immunomodulatory effects of degradation products must be thoroughly investigated. Additionally, nanozymes are prone to immune recognition processes, such as opsonization, complement activation, and uptake by antigen presenting cells. Their immunotoxic potential, which depends on surface properties, size, and dosage, can range from immunostimulation to severe inflammation [118].

To address these challenges, two main strategic approaches are essential. First, it is important to develop nanozymes with high biocompatibility, low toxicity, and clearly defined pharmacokinetics, including improved degradability and efficient clearance, to reduce post treatment retention and support green chemistry principles. Second, there is a critical need to establish standardized immunotoxicity evaluation methods, such as complement activation tests, cytokine profiling, dendritic cell and macrophage activation assays, and histopathology. Long term preclinical studies spanning multiple months should also be conducted, incorporating biodistribution analysis, functional tests, and material specific metabolic examinations. Unified immunotoxicological frameworks will play a key role in promoting the clinical translation of nanozyme technologies [119].

5.3. Expanding nanozyme diversity: Non-redox catalysts for synergistic probiotic-based therapy

To date, most probiotic nanozyme systems have utilized activities resembling those of oxidoreductases, which aligns closely with the need to counteract pathological oxidative stress [21,120]. For instance, in gastrointestinal diseases, oxidoreductase nanozymes scavenge ROS to alleviate inflammation, while in cancer therapy, they generate cytotoxic ROS to inhibit tumor growth [121,122]. In contrast, non-redox nanozymes, such as those mimicking hydrolases, remain largely unexplored in the context of probiotic integration. These catalysts, however, offer unique opportunities [123]. Protease-like nanozymes could remodel pathological extracellular matrices or disrupt pathogenic biofilms, thus promoting probiotic colonization. Glycosidase- or esterase- mimicking nanozymes may hydrolyze dietary polysaccharides or proteins into metabolites that support probiotic proliferation. Additionally, hydrolase-based activities could contribute to detoxifying harmful macromolecules within disease microenvironments [124]. A key challenge involves preventing off-target hydrolysis of probiotic cell walls. To address this issue, high-throughput screening or rational design can be prioritized to obtain hydrolytic nanozymes with high substrate specificity, thereby achieving precise control over their targets. For example, these nanozymes can selectively act on glycoproteins in the tumor extracellular matrix or polysaccharides in pathogenic biofilms, rather than performing indiscriminate broad cleavage. Another strategy is implementing spatiotemporal control through encapsulating hydrolytic nanozymes within stimuli responsive coatings such as pH, enzyme, or hypoxia sensitive materials to restrict activity to pathological microenvironments and spare probiotic structures. A further strategy is pairing specific strains with compatible nanozymes by screening probiotic strains with natural resistance to certain hydrolytic activities, such as those possessing robust exopolysaccharide layers or protective surface layer proteins, to ensure compatibility. Thus, although oxidoreductase nanozymes currently dominate the field, non-redox nanozymes represent a promising direction for probiotic assisted therapies and warrant further exploration.

Perspectives on optimizing probiotic-nanozyme coupling strategies, strengthening delivery and efficacy evaluation, and advancing personalized therapies and intelligent theragnostic systems are provided in Section S7 (Supporting information).

CRediT authorship contribution statement

Xiaoyu Fan: Writing – original draft. **Ergui Luo:** Writing – review & editing. **Wenjuan Wang:** Writing – review & editing. **Zhi Du:** Writing – review & editing, Writing – original draft, Resources, Project administration, Funding acquisition, Conceptualization. **Yi Deng:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Di Huang:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.112058.

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