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Review Article

Fermented Chinese Herbal Medicines Improve Intestinal Health in Livestock and Poultry via Microbial Transformation of Bioactive Compounds and Anti-Inflammatory Mechanisms

Yisheng ZHANG [1], Zhengshun WANG [1], DAWAQIONGDA [2], Hongming LIU [1], Yefen XU [1], Zeyan HUANG [1], Qinghui KONG [1 (*)]

[1] Xizang Agricultural and Animal Husbandry University,College of Animal Science, Nyingchi City, Xizang Autonomous Region, CHINA
[2] Zhongba County Agriculture,Animal Husbandry Integrated Service Center, Zhongba,Xizang Autonomous Region, CHINA

(*) **Corresponding author:**
Qinghui Kong
Phone: +86-13709767423
E-mail: kqh610@sina.com

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Abstract

Intestinal inflammation, underpinned by gut dysbiosis, epithelial barrier dysfunction and dysregulated TLR4/NF-κB-mediated innate immunity, represents a major constraint on livestock production efficiency and animal welfare. Traditional Chinese herbal medicines (TCHMs) possess multi-component, multi-target anti-inflammatory profiles and favourable safety margins; however, their therapeutic efficacy is limited by poor oral bioavailability, extensive first-pass metabolism and substantial pharmacokinetic variability. Microbial fermentation can remodel herbal constituents through polysaccharide depolymerisation, flavonoid glycoside hydrolysis, phenolic acid liberation and alkaloid/tannin modification, potentially yielding metabolites with improved bioaccessibility and intestinal anti-inflammatory activity. This narrative review synthesises current evidence on fermentation-mediated phytochemical transformation of Chinese medicinal herbs and the intestinal health effects of the resulting preparations in production animals. Fermentation microorganisms, metabolic profiles and condition-dependent phytochemical transformations are critically examined and integrated with tissue-level protective mechanisms encompassing gut microbiota remodelling, short-chain fatty acid metabolism, epithelial tight-junction reinforcement, suppression of aberrant TLR4/MyD88/NF-κB signalling and pathological NLRP3 inflammasome activation, as well as Nrf2-dependent antioxidant defence. Evidence obtained directly from fermented herbal preparations in production animals is explicitly delineated from that extrapolated from general probiotic or short-chain fatty acid (SCFA) literature. Importantly, much of the mechanistic evidence remains preclinical, and few studies have validated efficacy, optimal dosing or safety under commercial production conditions. Finally, a "strain-ingredient-metabolite-microbiota-host" mechanistic framework is proposed to guide the standardisation of fermentation protocols, quality control and the veterinary application of fermented TCHMs.

Keywords: Antioxidant defence, Chinese medicinal herbs, Gut microbiota, Microbial fermentation, Short-chain fatty acid

Introduction

Intestinal inflammation encompasses a spectrum of disorders hallmarked by mucosal barrier impairment, gut dysbiosis, and dysregulated innate immunity. In production animals, post-weaning diarrhoea (PWD) in piglets, frequently triggered by enterotoxigenic *Escherichia coli* (ETEC) infection and weaning stress, represents a leading cause of morbidity, growth retardation and economic loss in the swine industry [1,2]. Pathologically, ETEC-derived lipopolysaccharides and enterotoxins activate TLR4/MyD88/NF-κB signalling, driving TNF-α, IL-1β and IL-6 production whilst concurrently disrupting tight junction localisation and increasing epithelial permeability [3,4]. These convergent pathologies illustrate that intestinal inflammation emerges not from isolated cytokine dysregulation, but from the integrated collapse of microbiota homeostasis, barrier integrity and inflammatory control.

Traditional Chinese herbal medicines (TCHMs) offer multi-component, multi-target anti-inflammatory potential; however, their bioactive constituents -polysaccharides, flavonoid glycosides, saponins and alkaloids- are constrained

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by poor oral bioavailability. High molecular weight and extensive hydrogen bonding limit their bioaccessibility, i.e., release from the herbal matrix during gastro-intestinal digestion, whilst limited membrane permeability, extensive first-pass metabolism and microbiota-dependent metabolic variability further restrict the fraction reaching systemic circulation in an active form (i.e., bioavailability), resulting in negligible systemic exposure and highly inconsistent therapeutic responses [5-7]. For instance, oral ginsenosides exhibit absolute bioavailability below 5% [8], whilst most flavonoid glycosides require microbial deglycosylation prior to absorption [9]. Overcoming these bottlenecks of poor absorption, poor targeting and high metabolic variability is essential for realising the intestinal anti-inflammatory efficacy of TCHMs.

Microbial fermentation addresses these constraints through targeted bioconversion [10]. In production animals, fermented herbal preparations have demonstrated direct efficacy: a probiotic-fermented complex of *Radix isatidis*, *Radix scutellariae* and *Radix glycyrrhizae* reduces diarrhoea incidence and improves growth performance in weaned piglets [11]; fermented soybean meal attenuates ETEC K88-induced PWD by modulating inflammatory cytokines and caecal microbiota [12]; and fermented herbal feed additives enrich beneficial *Lactobacillus* whilst improving feed conversion in piglets [13]. Mechanistically, fermentation depolymerises polysaccharides into bioactive oligosaccharides, hydrolyses glycosides into membrane-permeable aglycones, and modifies alkaloids and tannins to attenuate toxicity whilst preserving bioactivity [14]. Murine dextran sulphate sodium (DSS)-colitis models further indicate that fermented *Astragalus* suppresses colonic TNF-α, IL-1β and IL-6, upregulates IL-10, and restores tight junction protein expression [15,16]. However, such murine findings serve solely as mechanistic explorations; their extrapolation to porcine PWD should be regarded as tentative given species-dependent differences in immune architecture, microbiota composition and disease pathogenesis-specifically, DSS induces chemical epithelial injury and Th1/Th17-mediated transmural inflammation, whereas porcine PWD is primarily driven by ETEC enterotoxins, fimbrial adhesion and weaning-induced barrier collapse [17].

Despite this growing body of work, the specific knowledge gap addressed by this review remains insufficiently served by the existing literature. Prior reviews of fermented TCHMs have been written primarily from phytochemical, pharmacological or human clinical perspectives, cataloguing component-content changes and *in vitro* bioactivities; the few reviews touching on animal production have largely listed growth-promoting effects without critically appraising the strength or origin of the underlying evidence [18-20]. Three unresolved gaps persist. First, evidence obtained directly from fermented herbal preparations in livestock and poultry has not been systematically separated from mechanisms extrapolated from rodent colitis models, cell-culture systems or the general probiotic and SCFA literature, leaving the actual strength of support for proposed intestinal mechanisms unclear. Second, fermentation variables (microbial strain, substrate, temperature, pH, moisture, oxygen availability and duration) have rarely been linked to the resulting metabolite profiles and intestinal outcomes, which hampers standardisation and reproducibility. Third, safety and quality-consistency concerns specific to veterinary use (including microbial contamination, mycotoxins, toxic metabolites and batch-to-batch variation) remain largely unaddressed.

To address these gaps, the present narrative review makes two distinctive contributions. First, it centres specifically on the production-animal intestinal anti-inflammation dimension, explicitly distinguishing evidence derived directly from Chinese fermented herbal preparations in livestock from mechanisms extrapolated from general probiotic, SCFA or murine colitis literature. Second, it advances a unified "strain-ingredient-metabolite-microbiota-host" mechanistic framework that integrates fermentation biotransformation with gut microbiota remodelling and host tissue-level pathways, providing a conceptual foundation for standardising fermentation protocols and advancing targeted microbial fermentation strategies in veterinary practice. *Fig. 1* provides an overview of this process: herbal materials are biotransformed by probiotic microbes into bioavailable metabolites that remodel gut microbiota, with downstream tissue level protective mechanisms presented in *Fig. 4*. The following sections examine fermentation microorganisms and metabolic profiles, condition-dependent phytochemical transformations, and gut anti-inflammatory mechanisms, before evaluating therapeutic efficacy in livestock production.

Literature Search and Review Methodology

This article is a narrative review; no systematic protocol was registered and the PRISMA framework was not applied. Literature was retrieved from PubMed, Web of Science, Scopus and CNKI up to June 2026, using combinations of terms covering fermentation ("fermentation", "biotransformation", "probiotic fermentation"), subject ("traditional Chinese medicine", "Chinese herbal medicine") and outcomes ("intestinal inflammation", "gut microbiota", "intestinal barrier", "weaned piglet", "broiler", "livestock"); reference lists of retrieved articles were

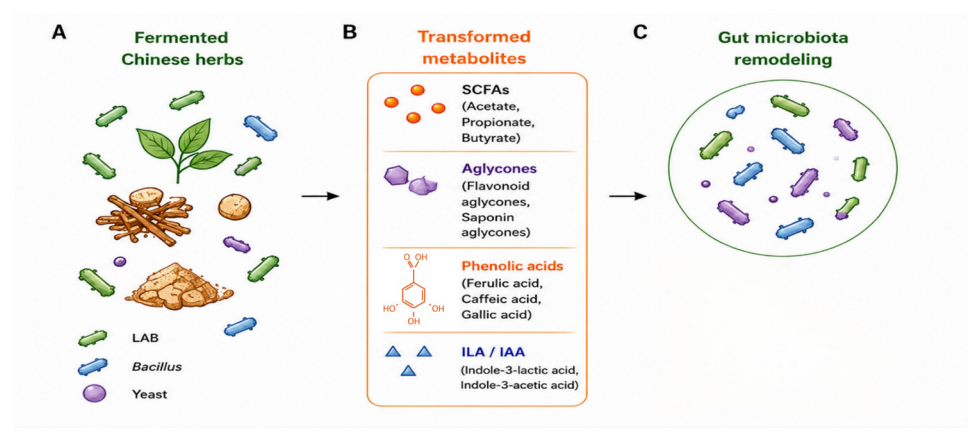

Fig 1. Overview of fermented Chinese herbal medicines and their bioactive metabolites. **(A)** Chinese herbal materials are fermented by lactic acid bacteria (LAB), *Bacillus* species, and yeasts, driving phytochemical biotransformation; **(B)** Fermentation produces diverse bioactive metabolites, including SCFAs, flavonoid and saponin aglycones, phenolic acids (ferulic acid, caffeic acid, gallic acid), and indole derivatives [indole-3-lactic acid (ILA) and indole-3-acetic acid (IAA)], which exhibit enhanced bioavailability and bioactivity relative to their pre-fermentation counterparts; **(C)** These metabolites remodel gut microbiota composition and maintain microbial homeostasis. Downstream tissue-level mechanisms underlying intestinal barrier reinforcement and immune modulation are detailed in *Fig. 4*

screened for additional sources. Peer-reviewed English or Chinese publications examining microbial fermentation of Chinese medicinal herbs and reporting phytochemical transformations, fermentation conditions, intestinal or anti-inflammatory outcomes, or production performance were included; conference abstracts, dissertations and non-fermentation studies were excluded. No formal risk-of-bias assessment was performed; instead, evidence is appraised qualitatively throughout, distinguishing data obtained directly in livestock and poultry from rodent, cell-culture and general probiotic/SCFA evidence, and demonstrated effects from proposed mechanisms.

Fundamentals of Microbial Fermentation and Biotransformation of Herbal Active Compounds

Microbial Strains and Metabolic Profiles in Chinese Herbal Fermentation

Chinese herbal fermentation typically employs *Lactobacillus*, *Bacillus* species, yeasts, and mixed microbial consortia. *Lactobacillus* produce lactic acid, acetic acid, exopolysaccharides, and glycoside hydrolases, thereby acidifying the fermentation substrate and facilitating glycoside biotransformation [21]. *Bacillus* species demonstrate robust stress tolerance and secrete proteases, amylases, cellulases, and pectinases, rendering them well suited for the fermentation of herbal residues and fibrous feedstocks. Chang et al.[22] developed a synbiotic formulation comprising probiotic-fermented herbal extracts and biogenic selenium nanoparticles, illustrating the field's transition from monostrain fermentation to polymicrobial synbiotic systems. Strain selection dictates the trajectory of biotransformation. Co-fermentation with *Lactobacillus acidophilus* and *Bacillus subtilis* enhances the bioactivity of honeysuckle-Cassia seed extracts [23]. Liao et al.[24] optimised *B. subtilis*-mediated fermentation of the 'Four Yellow' formula and assessed its anti-*Escherichia coli* efficacy and growth-promoting activity. These findings suggest that future Chinese herbal fermentation should move beyond conventional probiotics towards strain screening based on defined biotransformation capacity and targeted anti-inflammatory functionality.

Effects of Fermentation Conditions on Active Compound Biotransformation

Fermentation conditions critically govern enzyme activity and biotransformation efficiency, thereby determining product quality. Temperature and pH fluctuations directly modulate enzyme secretion profiles and catalytic stability. During solid-state fermentation, temperature gradually increases during spore germination, then rises sharply owing to metabolic heat generation during rapid growth. Concomitantly, pH initially increases due to protein deamination and NH_3 release, followed by a sharp decline as organic acids accumulate and NH_3 is consumed. This pH-temperature coupling governs the temporal dynamics of enzyme production: pectinases and invertases peak during rapid pH decline, whereas xylanase and α-galactosidase synthesis is markedly delayed [25]. pH directly modulates enzyme activity. For instance, recombinant AnGlu04478 exhibits optimal activity at pH 5.0 and retains substantial residual activity following 2 h incubation across pH 3.0-8.0. Its thermal optimum is

40°C, with robust stability between 25 and 50°C. Metal ions differentially modulate β-glucosidase activity: Na^+, K^+, Ca^{2+} and Mg^{2+} serve as activators or inhibitors, whereas SDS and EDTA consistently suppress enzyme function. Substrate induction also critically regulates enzyme secretion. For example, ginsenoside supplementation in *Aspergillus niger* fermentation markedly upregulates β-glucosidase gene expression, thereby enhancing rare ginsenoside biotransformation [26].

Moisture, oxygen availability and fermentation duration likewise shape biotransformation outcomes. Moisture governs substrate swelling, nutrient diffusion and enzyme secretion, and its optimum is strain-dependent: filamentous fungi tolerate low water activity, whereas bacteria and yeasts require 40-70% moisture [27,28]. Oxygen regime directs the transformation route-aerobic fungal processes favour oxidative bioconversion, whereas anaerobic lactic fermentation redirects metabolism towards organic acid accumulation [29]. Duration determines whether conversion halts at intermediates or reaches terminal metabolites, and over-incubation may degrade products through non-specific proteolysis [30]. These parameters act interactively, and their optimal windows are strongly strain-dependent *(Table 1)*.

Organic acid accumulation indirectly promotes polysaccharide hydrolysis by lowering environmental pH. Lactic acid, acetic acid, and other fermentation-derived organic acids alter polysaccharide molecular weight and functional properties through pH-dependent mechanisms. Distinct microbial communities generate unique acid profiles, resulting in divergent polysaccharide structural and functional modifications. Concomitantly, fermentation-generated free radicals attack glycosidic bonds and side-chain moieties, inducing polysaccharide cleavage and structural remodeling. Such modifications may unmask cryptic active sites, thereby enhancing antioxidant and immunomodulatory capacity [35].

Fermentation conditions also contribute substantially to poor inter-study reproducibility [36]. Variations in microbial strains, fermentation duration, or drying protocols applied to identical herbal materials yield divergent polysaccharide molecular weights, organic acid contents, and low-molecular-weight phenolic acid profiles. Fan et al.[37] compared the pro-digestive effects of *Massa Medicata Fermentata* (MMF) before and after processing, integrating metabolomic and microbiome analyses to demonstrate that processing methods concurrently modulate chemical composition and gut microbiota structure. Critically, most published studies report only a subset of relevant parameters; strain identity, moisture content and oxygen regime are the most frequently omitted, which not only accounts for much of the apparent inconsistency between studies but also precludes quantitative correlation of process parameters with metabolite outcomes. Claims that a given condition "enhances" bioactive transformation should accordingly be interpreted with caution unless the full parameter set is disclosed. Consequently, evaluating fermented Chinese herbal medicines requires a continuous evidence chain linking process parameters, metabolite profiles, and biological effects. Accordingly, *Fig. 2* delineates the interrelationships among microbial strains, fermentation conditions, and metabolites.

Effects of Fermentation on Bioactive Compounds in Chinese Herbal Medicines

Biotransformation of Polysaccharides and Glycosides

Polysaccharides constitute a critical material basis for the intestinal anti-inflammatory activity of Chinese

Table 1. *Comparison of the principal microbial groups used in herbal fermentation and their condition-dependent biotransformation profiles*

Microbial Group	Representative Genera	Key Enzymes	Typical Moisture/O_2 Regime	Major Biotransformations	Ref
Lactic acid bacteria	*Lactiplantibacillus*, *Lactobacillus*, *Pediococcus*	β-glucosidases, esterases, proteases	Higher moisture (40-70% in SSF); anaerobic/microaerophilic	Glycoside → aglycone hydrolysis; organic acid accumulation; phenolic liberation	[31]
Bacillus spp.	*B. subtilis*, *B. licheniformis*	Proteases, cellulases, amylases	Moderate-high moisture; aerobic	Cell-wall disruption and release of bound phenolics; glycoside hydrolysis; peptide generation	[32]
Yeasts	*Saccharomyces*, *Candida*	β-glucosidases, invertase	Moderate moisture; facultative anaerobic	Glycoside hydrolysis; flavour-active metabolite formation; ethanol/ester production	[31]
Filamentous fungi	*Aspergillus*, *Rhizopus*, *Monascus*	Cellulases, xylanases, pectinases, tannase, β-glucosidases	Low water activity tolerated; strictly aerobic, gas-exchange-dependent	Lignocellulose degradation; extensive glycoside→aglycone conversion; alkaloid modification	[26,33]
Mixed/co-culture consortia	LAB + yeast + *Bacillus* combinations	Complementary enzyme repertoires	Stepwise or simultaneous; regime depends on dominant member	Sequential transformations unattainable by single strains	[34]

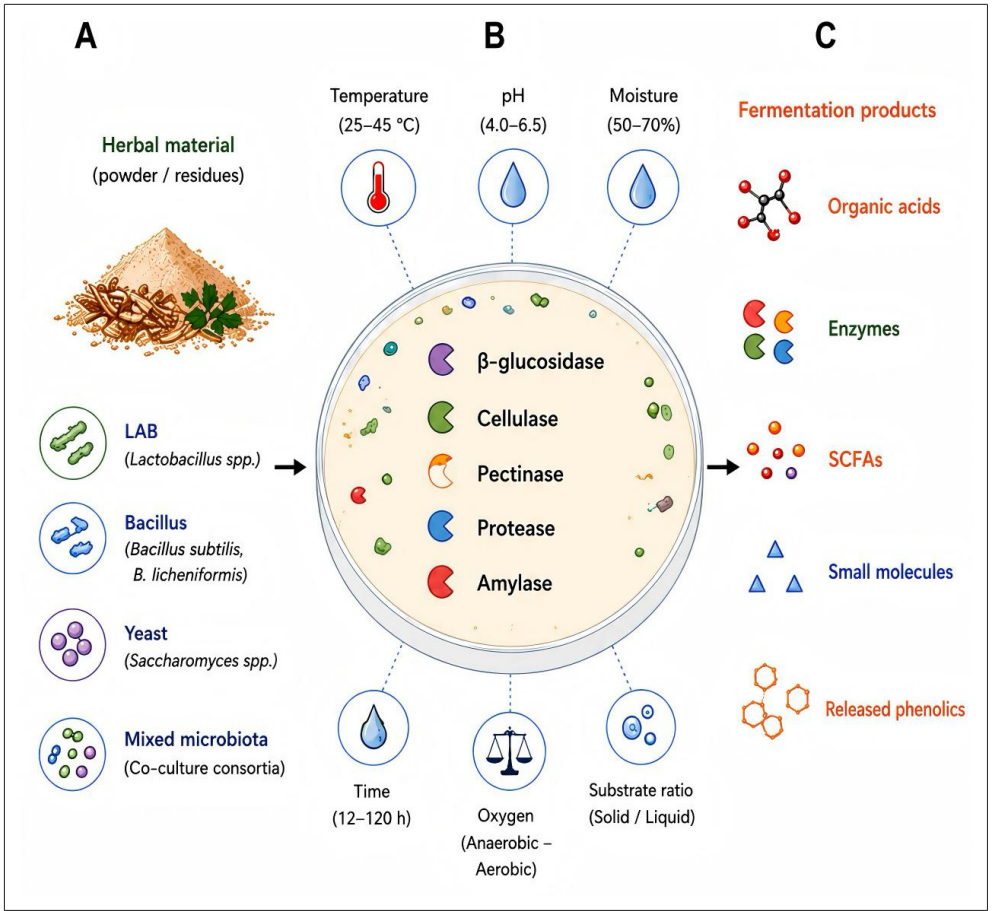

Fig 2. Microbial strains, fermentation conditions and metabolites during Chinese herbal fermentation. **(A)** *Lactobacillus, Bacillus* species, yeasts and mixed microbial consortia ferment Chinese herbal raw materials; **(B)** Under optimal conditions (temperature 25-35°C, pH 4.0-6.5, moisture 60-70%, fermentation duration 12-72 h, oxygen and substrate ratio), microorganisms secrete β-glucosidase, cellulase, pectinase, protease and amylase, promoting active constituent degradation and biotransformation. Fermentation condition ranges are based on typical operating parameters reported for probiotic-mediated solid-state fermentation of Chinese herbal materials [38-41]; **(C)** Fermentation generates organic acids, short-chain fatty acids (SCFAs), phenolic compounds, enzymes and other small-molecule bioactive substances, enhancing bioaccessibility and bioactivity

herbal medicines. Fermentation deploys polysaccharide hydrolases, cellulases, and pectinases to reduce polysaccharide molecular weight and increase soluble oligosaccharide content, thereby enhancing microbial utilisation. Yang et al.[38] demonstrated the prebiotic potential of fermented *Astragalus* polysaccharides, which modulate gut microbiota composition *in vitro*. Laoxianghuang polysaccharides also promote IL-10 production through gut microbiota-dependent linoleic acid metabolism [39]. These findings indicate that polysaccharide-mediated anti-inflammation relies on a sequential cascade from polysaccharide structure through microbial fermentation and metabolite generation to immune modulation. Glycoside biotransformation represents another critical mechanism for fermentation-enhanced bioavailability. Many flavonoids, saponins, and anthraquinones occur naturally as glycosides, which are highly polar and poorly absorbed [40]. Fermentation-derived β-glucosidases liberate aglycones, a transformation experimentally demonstrated by direct compositional analyses [41-44]; by contrast, the subsequent epithelial absorption and inflammatory target engagement of the liberated aglycones remain largely inferred from studies of isolated, non-fermented compounds and have rarely been demonstrated for fermented preparations themselves. Ma et al.[41] screened flavonoid glycoside-hydrolysing strains for the bioconversion of Shuanghuanglian medicinal residue, enabling its valorisation. This study underscores that targeted screening of biotransformation-capable strains is pivotal for elucidating fermentation-enhanced efficacy.

Biotransformation of Flavonoids, Phenolic Acids, and Alkaloids

Flavonoids and phenolic acids represent the predominant bioactive classes underpinning the anti-inflammatory efficacy of fermented Chinese herbal medicines [42]. Fermentation releases conjugated phenolic acids, remodels

flavonoid glycoside-to-aglycone ratios, and generates novel phenolic metabolites [43]. Metabolomic analyses have documented marked phenolic remodelling during MMF fermentation, with differential metabolites primarily categorised into lipids, amino acids, phenolic acids, organic acids, flavonoids and alkaloids; structural equation modelling further identified *Bacillus velezensis* and fungal species as key drivers of flavonoid and phenolic acid accumulation [44]. Zhang et al.[45] demonstrated that chebulagic acid ameliorates DSS-induced colitis while restoring gut microbiota homeostasis and attenuating oxidative stress. It should be emphasised that chebulagic acid evidence derives from the DSS colitis model; its direct applicability to porcine ETEC-PWD remains speculative and requires species-specific validation.

Alkaloid biotransformation is highly dependent on both the herbal matrix and the microbial strain employed. Certain alkaloids undergo deglycosylation, demethylation, redox reactions, and conjugation, thereby modulating their polarity, toxicity, and anti-inflammatory potential. Investigations into intestinal absorption and component interactions in Forsythia-Honeysuckle formulae reveal potential absorptive and metabolic interplays among constituents [46]. Consequently, evaluating alkaloid-containing fermented formulations necessitates assessment beyond total alkaloid content to encompass constituent ratios, metabolite profiles, and safety.

Effects of Fermentation on Active Compound Physicochemical Properties

Fermentation modulates the molecular weight, solubility, acid-base properties, stability, and bioaccessibility of herbal bioactive compounds. Polysaccharide degradation enhances solubility and microbial fermentability; glycoside hydrolysis remodels polarity and membrane permeability; organic acid generation acidifies the microenvironment and suppresses pathogenic proliferation. Bai et al.[47] demonstrated that MMF modulates gut microbiota composition in rats with functional dyspepsia; as detailed above, Fan et al.[37] and Zheng et al.[44] concurrently established that MMF fermentation remodels phenolic metabolite profiles and microbial community structure. Fermentation also potentiates the anti-inflammatory activity of ox bile through NLRP3 inflammasome suppression [48]. Collectively, these findings indicate that physicochemical remodelling ultimately translates into microecological and immunological outcomes. *Fig. 3* delineates the biotransformation pathways and functional enhancement mechanisms of key bioactive compounds during fermentation. Overall, polysaccharide depolymerisation and glycoside-to-aglycone hydrolysis are supported by direct compositional evidence, whereas most downstream functional attributions remain proposed mechanisms that await targeted experimental validation.

Research Progress on the Enhancement of the Biological Activity of Traditional Chinese Medicinal Herbs Through Fermentation

In terms of biological activity, fermented Chinese herbal medicines primarily exhibit anti-inflammatory, antioxidant, gut microbiota-regulating and gut barrier-enhancing effects. Existing research has shown that fermented herbal preparations can exert protective effects both *in vivo* and *in vitro* under LPS stimulation [49]; fermented Pueraria root extract can alleviate DSS-induced colitis by reducing pro-inflammatory cytokine levels [50] fermented *Astragalus* and its metabolites modulate inflammatory states, improve gut microbiota structure and promote intestinal barrier repair in DSS colitis mice [51]. These murine mechanistic insights, while informative, should not be equated with fermented-herb efficacy in porcine PWD, given the divergent aetiologies of chemical colitis versus bacterial enterotoxigenic diarrhoea. These results indicate that the synergistic effects of fermentation are not only reflected in the transformation and enhancement of bioactive components, but are also further demonstrated by improvements in the host's inflammatory response and intestinal function.

Mechanisms of Action of Fermented Chinese Herbs in Intestinal Anti-Inflammation

Regulation of Gut Microbiota Composition and Metabolic Function

The gut microbiota is a key determinant of host health. A healthy gut microbiota typically exhibits high diversity, high gene richness, and stable metabolic function, all of which are crucial for maintaining intestinal homeostasis [52]. Disruption of the gut microbiota following weaning is a major cause of diarrhoea in piglets. Using 16S rRNA sequencing, Konstantinov et al.[53] and Lu et al.[54] analysed gut microbiota composition and metabolic shifts in piglets during the neonatal and weaning periods. The results indicated that the gut microbiota of neonatal piglets (2-12 days) was dominated by *E. coli* and various *Lactobacillus* species, with *Lactobacillus* predominating during the pre-weaning stage. Lactic acid and acetic acid produced by these bacteria maintain a low gut pH, thereby inhibiting pathogen colonisation. However, following weaning, *Lactobacillus* abundance declined significantly, whilst levels of potential pathogens, represented by *Clostridium* and *Escherichia,* gradually increased. This indicates that weaning significantly alters gut microbiota structure and metabolic activity, potentially increasing the risk of dysbiosis and diarrhoea. Such changes weaken lactic acid- and bacteriocin-mediated antibacterial effects, thereby reducing colonisation resistance against pathogenic bacteria.

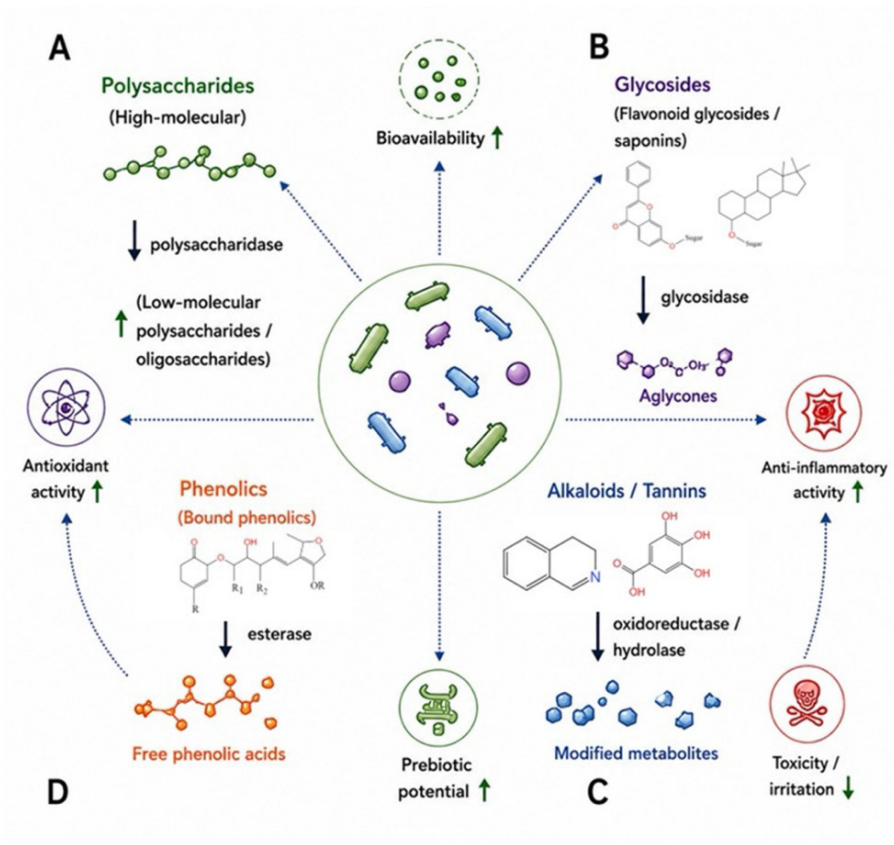

Fig 3. Overview of microbial biotransformation of major bioactive compounds during the fermentation of Chinese herbal materials. **(A)** Microbial polysaccharidases degrade high-molecular-weight polysaccharides into low-molecular-weight oligosaccharides, enhancing their biological activity; **(B)** Microbial glycosidases hydrolyze glycosidic bonds in flavonoid glycosides and steroidal saponins (representative skeletons shown) to release aglycones with improved bioavailability; **(C)** Microbial oxidoreductases and hydrolases modify alkaloids and tannins (representative skeletons shown), generating metabolites with enhanced functionality and reduced toxicity; **(D)** Microbial esterases hydrolyze bound phenolics to release free phenolic acids, increasing antioxidant capacity. These transformations collectively improve bioavailability, prebiotic potential, and bioactivity while reducing undesirable effects

In terms of gut microbiota regulation, fermented Chinese herbal medicines selectively enrich beneficial commensals that produce short-chain fatty acids [55]. Fermented bamboo shoots increase the abundance of *Akkermansia, Anaerovorax* and *Bacteroides* in the gut of DSS-induced colitis mice, while reducing the disease activity index [56]. Extrapolation of such murine DSS-colitis findings to porcine post-weaning diarrhoea should be regarded as tentative, given species- and model-dependent differences in pathogenesis, immune architecture and microbiota composition [57]. *Lactobacillus helveticus* H3 restores *Lactobacillus* and *Bifidobacterium* populations suppressed by pathogenic *E. coli*, while reducing *Escherichia-Shigella* colonization [58]. Fermentation-derived polyphenolic metabolites also serve as selective growth factors for *Lactobacillus* and *Bifidobacterium,* while inhibiting pathogens such as *Clostridioides* difficile and *E. coli* [59]. *Akkermansia muciniphila,* a mucin-degrading bacterium, produces acetate, butyrate and propionate; its abundance negatively correlates with disease activity index and pro-inflammatory factor levels [60]. It must be stressed that these microbiota shifts are largely correlational: compositional changes demonstrated by 16S rRNA profiling do not, by themselves, establish a causal contribution to improved intestinal health. Direct mechanistic evidence for fermented herbal interventions -such as faecal microbiota transplantation or germ-free validation- remains scarce; a notable exception is the transplantation-validated tryptophan-metabolite pathway discussed below [61].

At the metabolite level, SCFAs, including acetate, propionate and butyrate, are key anti-inflammatory molecules derived from dietary fibre fermentation by intestinal beneficial bacteria [61]. As the primary energy source for colonic epithelial cells, butyrate exerts anti-inflammatory effects principally through GPR109A activation and histone deacetylase (HDAC)

inhibition, while its induction of Treg differentiation and IL-10 production is largely independent of NLRP3 inflammasome activation [62,63]. Functionally, butyrate strengthens intestinal epithelial barrier integrity by upregulating tight junction proteins (claudin-1, ZO-1 and occludin) via AMPK activation and alleviates cytokine-induced barrier injury by downregulating claudin-2 [64-66]. These protective effects have been validated in weaned piglets, where supplemental butyrate improved intestinal tight junction structure and reduced the incidence of post-weaning diarrhoea [67]. Notably, direct evidence supporting the barrier-protective and anti-inflammatory functions of herbal fermentation-derived butyrate against porcine PWD remains insufficient [68]. Unlike butyrate, acetate and propionate act mainly through GPR43 to trigger physiological NLRP3 inflammasome activation and subsequent IL-18 maturation, which sustains epithelial homeostasis and differs from pathological NLRP3 activation in intestinal inflammation [69]. Additionally, butyrate facilitates inflammation resolution by inducing Foxp3 Treg cells and IL-10 secretion via GPR43/GPR109A signalling and HDAC inhibition [70]. Moreover, propionate relieves intestinal inflammation by suppressing IL-8 and VCAM-1 expression through HDAC inhibition, whereas acetate primarily mediates epithelial protection via GPR43 signalling [62].

Beyond SCFAs, tryptophan metabolites such as indole-3-lactic acid (ILA) and indole-3-acetic acid (IAA) constitute another vital mechanistic axis underlying the beneficial effects of fermented Chinese herbal medicines. Solid-state fermented *Lacticaseibacillus paracasei* cultures enrich ILA and IAA, activate aryl hydrocarbon receptor (AhR) signalling and strengthen the mucosal barrier-effects abolished by antibiotic-induced microbiota depletion yet restored by faecal microbiota transplantation or metabolite supplementation [71,72]. These tryptophan metabolites stimulate the expression of IL-22, mucins and antimicrobial peptides via AhR activation, facilitating intestinal barrier repair and homeostasis [72,73].

Intestinal Barrier Function Improvement

Intestinal barrier damage is a key step in the progression from microbial dysbiosis to clinical diarrhoea. The intestinal barrier comprises mechanical, chemical, immune and biological barriers, with the mechanical barrier serving as the first line of defence against pathogen and harmful substance invasion [74]. Normal barrier integrity is maintained by the mucus layer, epithelial cells, tight junctions and mucosal immunity. Weaning stress reduces energy intake and epithelial renewal capacity in piglets, leading to decreased villus height and crypt hyperplasia, ultimately compromising intestinal barrier integrity. Liu et al. [75] and López-Colom et al.[76] demonstrated that enterotoxins, lipopolysaccharides and pro-inflammatory factors produced by enterotoxigenic *E. coli* (ETEC) damage the intestinal mucosal layer and tight junction structures, increasing permeability and ultimately triggering intestinal inflammation.

Fermented Chinese herbal medicines repair the intestinal mucosal barrier through multiple mechanisms, as illustrated in *Fig. 4*, including upregulating tight junction protein expression, suppressing aberrant immune activation and enhancing mucosal immunity. Tight junction proteins are key molecules maintaining intestinal epithelial physical barrier integrity; fermentation products promote tight junction protein expression by regulating Hippo/YAP and PI3K/Akt/mTOR signalling pathways [77]. For example, in a direct production-animal study, a fermented herbal formulation (FHF) composed of Radix isatidis, Folium isatidis, Radix scutellariae, Fructus forsythiae and Radix glycyrrhizae -fermented with Enterococcus faecium and *Saccharomyces cerevisiae*-upregulated Claudin-1, Occludin and ZO-1 expression at both mRNA and protein levels in the jejunum of weaned piglets, concomitantly reducing serum diamine oxidase (DAO) and TNF-α levels [4]. Fermented plant extract (FPE) significantly reduces intracellular ROS levels in IPEC-J2 intestinal epithelial cells, restoring barrier integrity and cell migration capacity, indicating direct barrier-protective effects of fermented Chinese herbal medicines [78]. Importantly, increased expression of barrier-related proteins alone does not necessarily demonstrate improved intestinal permeability; functional evidence is available for only a subset of preparations, and most studies lack direct permeability measurements such as FITC-dextran flux, transepithelial electrical resistance or serum D-lactate.

Concurrently, as depicted in *Fig. 4-C*, fermentation-derived metabolites suppress aberrant TLR4/MyD88/NF-κB signalling and pathological NLRP3 inflammasome activation in lamina propria immune cells, thereby reducing pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and promoting anti-inflammatory IL-10 production [4]. Notably, while these signalling pathways are well characterised in general intestinal immunology, their direct inhibition by fermented herbal metabolites has been specifically demonstrated in LPS-stimulated IPEC-J2 cells and weaned piglets for FHF, and in THP-1 macrophages for fermented plant extracts [78]; extrapolation to other fermented preparations or species should remain cautious. Moreover, activation of the Nrf2 antioxidant pathway enhances HO-1, SOD and GPX expression, further reducing ROS accumulation and attenuating intestinal inflammation *(Fig. 4)* [79]. At the mucosal immunity level, enrichment of beneficial bacteria such as *A. muciniphila* increases mucus layer thickness, protects intestinal mucosal integrity and maintains immune homeostasis [60]. Furthermore, fermentation products enhance intestinal

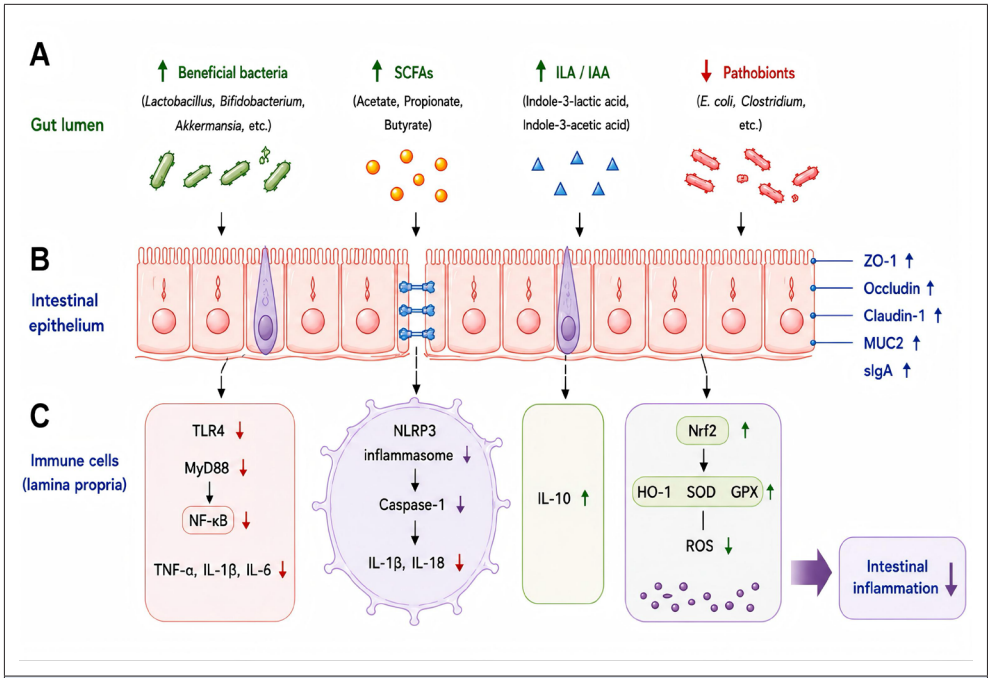

Fig 4. Tissue-level mechanisms of fermented herbal metabolites in alleviating intestinal inflammation. **(A)** In the gut lumen, fermentation-derived SCFAs, indole-3-lactic acid (ILA), and indole-3-acetic acid (IAA) enrich beneficial bacteria (*Lactobacillus, Bifidobacterium, Akkermansia*) whilst suppressing pathobionts (E. coli, Clostridium); **(B)** These metabolites reinforce epithelial barrier integrity by upregulating tight junction proteins (ZO-1, occludin, claudin-1), mucin-2 (MUC2), and secretory IgA (sIgA), **(C)** In the lamina propria, metabolites suppress aberrant TLR4/MyD88/NF-κB signalling and pathological NLRP3 inflammasome activation, thereby reducing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and promoting anti-inflammatory IL-10 production. Concurrently, Nrf2-mediated antioxidant defence (HO-1, SOD, GPX) is activated to reduce ROS accumulation. These coordinated actions collectively attenuate intestinal inflammation and restore mucosal homeostasis

chemical barrier function by promoting sIgA secretion, and maintain lamina propria immune cell homeostasis by regulating dendritic cell maturation and Treg/Th17 balance, thereby synergistically repairing the intestinal mucosa at both structural and immune barrier levels [69]. Collectively, these coordinated actions at the epithelial and immune levels synergistically restore intestinal mucosal homeostasis *(Fig. 4)*. Nevertheless, it must be acknowledged that strong correlation with weak causality remains a limitation: microbiota changes may be either the cause or consequence of inflammation, and increased SCFA levels may directly protect the barrier or may simply accompany beneficial bacterial enrichment without proven causality in the context of fermented herbal interventions.

Modulating Inflammatory Response and Oxidative Stress

The immune-inflammatory response is also a key factor in post-weaning diarrhoea development in piglets. LPS is recognised by TLR4 and activates MyD88, IKK and NF-κB signalling, leading to TLR4 and NF-κB upregulation and subsequent induction of pro-inflammatory cytokines including TNF-α, IL-1β and IL-6. NF-κB activation not only promotes inflammatory factor release but also affects tight junction protein localisation and epithelial cell apoptosis [80]. Fermentation-derived metabolites suppress aberrant TLR4/MyD88/NF-κB signalling and pathological NLRP3 inflammasome activation, thereby reducing TNF-α, IL-1β and IL-6 production whilst promoting anti-inflammatory IL-10 secretion and Nrf2-mediated antioxidant responses *(Fig. 4)*. Thus, TLR4/NF-κB signalling modulation alleviates inflammation and serves as a key pathway linking pathogen expansion, exacerbated inflammation and barrier disruption. The JAK-STAT pathway is also involved in mucosal immune regulation following weaning stress in piglets [81].

Fermented Chinese herbal medicines block the intestinal inflammatory cascade by inhibiting pro-inflammatory signalling pathways, activating antioxidant defence systems and restoring the balance between pro- and anti-inflammatory factors [69]. It should be noted that many of these anti-inflammatory mechanisms are derived from general SCFA and polyphenol literature; where effects are demonstrated specifically with fermented herbal preparations, this is indicated explicitly. Regarding pro-inflammatory pathway inhibition, fermentation products act on mitogen-activated protein kinase and nuclear factor κB signalling. Extracts from fermented and aged mountain-cultivated ginseng shoots inhibit phosphorylation of extracellular signal-regulated kinase,

p38 and c-Jun N-terminal kinase in lipopolysaccharide-stimulated RAW 264.7 macrophages, and prevent NF-κB p65 nuclear translocation, thereby reducing production of pro-inflammatory mediators including TNF-α, IL-1β, IL-6 and inducible nitric oxide synthase [82]. In THP-1 macrophages, fermented plant extracts inhibit nuclear factor κB activation via a Toll-like receptor 4-independent pathway, downregulating pro-inflammatory factors including tumour necrosis factor-α and monocyte chemotactic protein, while upregulating anti-inflammatory IL-10 [78]. *Lactobacillus* fermented ginseng sprout extract also inhibits lipopolysaccharide-induced nitric oxide and prostaglandin E2 production, and downregulates cyclooxygenase-2 and pro-inflammatory cytokine expression.

Regarding antioxidant stress, fermentation products activate the nuclear factor E2-related factor 2 (Nrf2)/antioxidant response element (ARE) signalling pathway. Under oxidative stress, Kelch-like ECH-associated protein 1 (Keap1) undergoes conformational changes, enabling Nrf2 dissociation, stabilisation and nuclear translocation. Following heterodimerisation with small Maf proteins, Nrf2 binds to ARE, thereby initiating transcription of downstream antioxidant enzymes including haem oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1, superoxide dismutase and glutathione peroxidase [83]. Direct *in vivo* evidence for fermented herbal preparations in production animals demonstrates that one fermented herbal formulation upregulates Nrf2 and downstream antioxidant enzymes while decreasing MDA concentrations in weaned piglets [84]. Nevertheless, much of the canonical Nrf2/ARE signalling framework described above originates from general oxidative stress research and investigations using non-fermented herbal compounds. Traditional herbal formulations such as Gegen Qinlian Decoction counteract oxidative stress by activating the Nrf2/ARE pathway, with puerarin, berberine and glycyrrhizin as the primary active drivers [85]. A distinction is warranted between direct antioxidant effects -radical scavenging by fermentation-liberated phenolics, demonstrated largely in cell-free or cell-culture assays- and activation of endogenous antioxidant defence via the Nrf2/HO-1 axis, for which *in vivo* production-animal evidence remains limited to a small number of trials [84]. The former cannot be assumed to translate into *in vivo* redox modulation.

Notably, Nrf2 and NF-κB pathways exhibit reciprocal cross-regulation [86]. The NF-κB p65 subunit inhibits the Nrf2 pathway by competitively binding the transcriptional co-activator cyclic adenosine monophosphate response element-binding protein (CREB), or by recruiting histone deacetylase 3 (HDAC3) to induce local deacetylation [87]. Conversely, Nrf2 activation also suppresses NF-κB transcriptional activity. By simultaneously regulating these two pathways, fermented Chinese herbal medicines reduce pro-inflammatory factor production (TNF-α, IL-1β, IL-6), while promoting anti-inflammatory interleukin-10 expression, thereby restoring the dynamic balance between pro- and anti-inflammatory factors. Based on microbiota, barrier, inflammatory and oxidative stress mechanisms, *Fig. 4* summarises the key mechanisms by which fermentation-derived metabolites alleviate intestinal inflammation.

Application of Fermented Chinese Herbal Medicines in Intestinal Inflammation

Applications in Livestock and Poultry Production

Available evidence from production-animal studies indicates that specific fermented herbal preparations exert species- and formulation-dependent effects on intestinal health and production performance, though the breadth of evidence varies considerably across livestock classes *(Table 2)*.

In pigs, fermentation of Chinese herbal mixtures and composite preparations has been associated with improved growth performance and reduced diarrhoea incidence in weaned piglets challenged by weaning stress or enterotoxigenic *E. coli* [93,94]. A recent study demonstrated that a fermented herbal formulation (FHF) containing *Radix isatidis*, *Folium isatidis*, *Radix scutellariae*, *Fructus forsythiae* and *Radix glycyrrhizae* -fermented with *Enterococcus faecium* and *Saccharomyces cerevisiae*- improved average daily gain, reduced diarrhoea rate, enhanced jejunal tight junction protein expression (Claudin-1, Occludin, ZO-1), elevated acetic and butyric acids, and enriched *Limosilactobacillus* and *Lactobacillus* in weaned piglets [85]. These effects appear to be mediated through concurrent modulation of gut microbiota composition, enhancement of tight junction protein expression and attenuation of systemic inflammatory markers such as TNF-α [84,94]. Fermented herbal extracts have also been reported to improve nutrient digestibility during critical growth phases and to reduce environmental ammonia and hydrogen sulphide emissions in commercial pig production. Consistent with these findings, dietary supplementation with fermented Chinese herbal medicine feed additives improved growth performance and intestinal microbiota composition in weaned piglets [95], and probiotics-fermented Massa Medicata Fermentata ameliorated weaning stress by restoring intestinal homeostasis [96].

In poultry, *Clostridium perfringens*-induced necrotic enteritis (NE) remains a major enteric disease, with

Table 2. *Comparative effects of fermented herbal preparations in production animals*

Fermented Preparation	Fermentation Strain/Inoculum	Animal Model (challenge, if any)	Primary Endpoint(s)	Key Outcome(s)	Ref.
Chinese herbal mixture (4 kg/t diet)	Not specified	Weaned piglets	Growth performance, diarrhoea incidence	↑ Final weight, ↑ ADG, ↓ F/G ratio, ↓ diarrhoea incidence	[85]
FHF (Banlangen, Lianqiao, Huangqin, Gancao; 0.6% diet)	Probiotic consortium	Weaned piglets	Growth, serum inflammation, intestinal barrier, caecal microbiota	↑ Final body weight, ↑ ADG, ↓ FCR, ↓ diarrhoea, ↓ serum TNF-α and DAO, ↑ jejunal tight junction proteins, ↑ *Limosilactobacillus* and *Lactobacillus*	[4]
Fermented herbal extract (FHE)	Not specified	Weaning and fattening pigs	Nutrient digestibility, faecal gas emissions	Improved digestibility, ↓ ammonia and hydrogen sulphide emissions	[88]
Fermented cottonseed meal (8% diet)	Not specified	Broilers	Weight gain	↑ Weight gain by 3-4%	[89]
Fermented rapeseed meal (50% soybean meal replacement)	Not specified	Broilers	Weight gain, FCR	↑ Weight gain by 6-24%, ↓ FCR by 6-18%	[89]
Thymol/carvacrol (plant-derived additives)	Not specified	NE-challenged broilers	NE lesion scores, mortality	↓ Lesion scores, ↓ mortality	[90,91]
Fermented Chinese herbal additive	Probiotic consortium	Beef cattle	ADG, FCR, faecal pathogens	↑ ADG, ↓ FCR, ↓ faecal pathogen loads	[92]

estimated annual economic impacts exceeding several billion US dollars [95,96]. Fermented feed ingredients -including cottonseed meal and rapeseed meal- have shown potential in ameliorating NE-associated growth depression and intestinal lesions [95]. Additionally, plant-derived bioactive compounds such as thymol and carvacrol, whether delivered directly or via fermentation matrices, appear to reduce NE lesion scores and mortality through antimicrobial and immunomodulatory actions [91]. It should be noted that most poultry-related findings were obtained using fermented feed ingredients, not fermented Chinese herbal medicines as the test material. Caution is therefore required when extrapolating results to other plant species. More directly, dietary supplementation with fermented *Astragalus* powder improved growth performance and health status in broiler chickens [97].

In ruminants, research on fermented Chinese herbal medicines remains comparatively limited. Existing studies suggest that probiotic-fermented herbal additives may improve average daily gain and feed conversion efficiency in weaned lambs, whilst favourably modulating serum biochemistry and the intestinal microbiome [98]. Butyrate-producing fermentation consortia have also been implicated in enhancing ruminal epithelial barrier function and attenuating systemic inflammatory markers. However, the evidence base is insufficient to draw definitive conclusions regarding rumen-gut axis inflammation, and further species-specific trials are warranted.

Collectively, these studies demonstrate that the efficacy of fermented herbal interventions is highly dependent on the specific botanical matrix, fermentation strain, animal model and endpoint examined *(Table 2)*. Rather than supporting a generalised claim that "fermented herbs are effective," the data highlight the need for standardised, comparative evaluation of distinct preparations across defined production contexts.

Research Progress in Experimental Models of Enteritis

Experimental colitis models provide controlled conditions for mechanistic studies. The DSS colitis model is commonly used to evaluate epithelial damage, dysbiosis and inflammatory pathways [97]. Fermented *Astragalus* and its metabolites modulate inflammatory status and gut microbiota in DSS colitis mice, whilst repairing the intestinal barrier [51]. Fermented Pueraria root extract reduces pro-inflammatory cytokines and alleviates DSS colitis [50]. Zhang et al.[45] found that chebulagic acid ameliorates oxidative stress, inflammation and gut microbiota dysbiosis in DSS colitis.

Beyond the DSS model, the 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis model represents a well-established chemically-induced model that mimics key features of Crohn's disease, including transmural inflammation, Th1-dominant immune responses and granuloma formation [98]. In TNBS-induced colitis, rectal administration of TNBS in ethanol disrupts the colonic mucosal barrier and haptenates colonic proteins, triggering a T-cell-mediated delayed-type hypersensitivity response characterised by elevated interferon-γ (IFN-γ), TNF-α and IL-12 production [99,100]. Fermented Chinese herbal medicines have demonstrated protective efficacy in this model through multiple mechanisms. Lian-Zhi-Fan (LZF) solution, a fermented preparation of Coptidis Rhizome, Gardeniae Fructus and alum, significantly ameliorates

body weight loss, disease activity index (DAI) score and colonic histopathological injury in TNBS-induced colitis rats [101]. Metabolomics analysis revealed that LZF modulates amino acid metabolism (L-alanine, L-valine), primary bile acid biosynthesis (cholic acid, taurocholic acid) and nicotinate/nicotinamide metabolism, thereby restoring energy production and attenuating inflammatory responses [102]. Additionally, berberine, a representative alkaloid from Coptidis Rhizome, attenuates TNBS-induced colitis by inhibiting inflammatory responses and Th1/Th17 differentiation, concomitantly with modulation of intestinal microbiota composition [101]. In a *Lactobacillus brevis* AL0035 fermentation study, oral administration of the probiotic strain counteracted TNBS-induced body weight loss, reduced DAI and histological injury scores, and decreased mRNA and protein expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, IFN-γ) whilst enhancing IL-10 expression [103,104] Furthermore, AL0035 restored microbial diversity depleted by TNBS administration, increased the relative abundance of *Lactobacillaceae* and *Lachnospiraceae*, and decreased *Proteobacteria* abundance, indicating that fermentation-derived metabolites alleviate TNBS colitis through coordinated regulation of inflammatory cytokines, tight junction protein expression (ZO-1) and gut microbiota composition [105]. These findings collectively demonstrate that fermented Chinese herbal medicines exert intestinal protective effects in the TNBS model via immunomodulation, barrier repair and microbiota restoration, consistent with mechanisms observed in DSS and other colitis models.

The LPS stimulation model, antibiotic-induced injury model, *Salmonella gastroenteritis* model and intestinal ischaemia-reperfusion model are also employed to evaluate intestinal inflammation. Bose et al. utilised LPS stimulation to validate the protective effects of fermented herbal preparations [49], and demonstrated in a separate study that herbal preparations counteract neomycin-induced intestinal injury [102]. These models illustrate the intestinal protective potential of Chinese herbal medicines and their fermentation products from various perspectives, including pathogen-induced damage, drug-induced injury and barrier ischaemia.

Comparison and Evaluation of the Application Effects of Fermented Herbal Medicines

Evaluation focus for fermented Chinese herbal medicines varies across models. Production animal studies emphasise growth performance, diarrhoea, gut health, microbiota and immune parameters, whereas experimental colitis models focus on histopathology, inflammatory cytokines, oxidative stress and barrier proteins. Piglet studies by Wang et al.[4] and Chen et al.[85] align more closely with practical animal production applications. DSS-induced colitis research presents a more comprehensive mechanistic chain, demonstrating that fermented *Astragalus* simultaneously influences inflammation, microbiota and intestinal barrier integrity [51]. TNBS-induced colitis studies provide complementary evidence for Th1-mediated immune modulation and transmural inflammation, with fermented preparations such as LZF solution and berberine demonstrating efficacy through metabolic pathway regulation and microbiota restoration [97]. Chebulagic acid studies, meanwhile, are more helpful in confirming the anti-inflammatory basis of specific *Terminalia chebula* components [45].

Medicinal herbs also differ in their fermentation outcomes. *MMF* research focuses on traditional fermented medicines, digestive function and microbiome regulation [106], as detailed in preceding sections. Fermented *Astragalus* research, meanwhile, emphasises polysaccharides, prebiotic effects, immunomodulation and barrier repair [51]. Co-fermented Chinese herbal medicine by-product research demonstrates that herbal residues yield antioxidant and anti-inflammatory benefits following appropriate fermentation [104]. Therefore, a blanket statement that 'fermented Chinese herbal medicines are effective' is inaccurate; rather, specific herbal materials, strains, metabolites, inflammatory models and evaluation endpoints must be clearly defined. Drawing on evidence from livestock and poultry production, experimental enteritis models and cellular studies, *Fig. 5* summarises the distribution of research evidence for the intestinal protective effects of fermented Chinese herbal medicines.

Safety, Standardisation and Commercial Applicability

The safety profile of fermented Chinese herbal medicines requires explicit consideration before routine veterinary application. Herbal raw materials and improperly controlled fermentations are vulnerable to microbial contamination and mycotoxins, which remain endemic in feed supply chains and can impair animal health and enter the food chain [107,108]. Although fermentation can degrade antinutritional factors and certain mycotoxins [15,16], uncontrolled fermentation may equally generate toxic metabolites or biogenic amines, and batch-to-batch variability in herbal starting materials further complicates safety evaluation [92,107]. Adverse effects have rarely been reported in the studies reviewed here, but they have also rarely been monitored systematically; future trials should incorporate explicit safety endpoints, including mycotoxin screening, microbial limits and histopathological examination [107,108].

Standardisation is a prerequisite for reproducible efficacy. Future studies should report, as a minimum: (i)

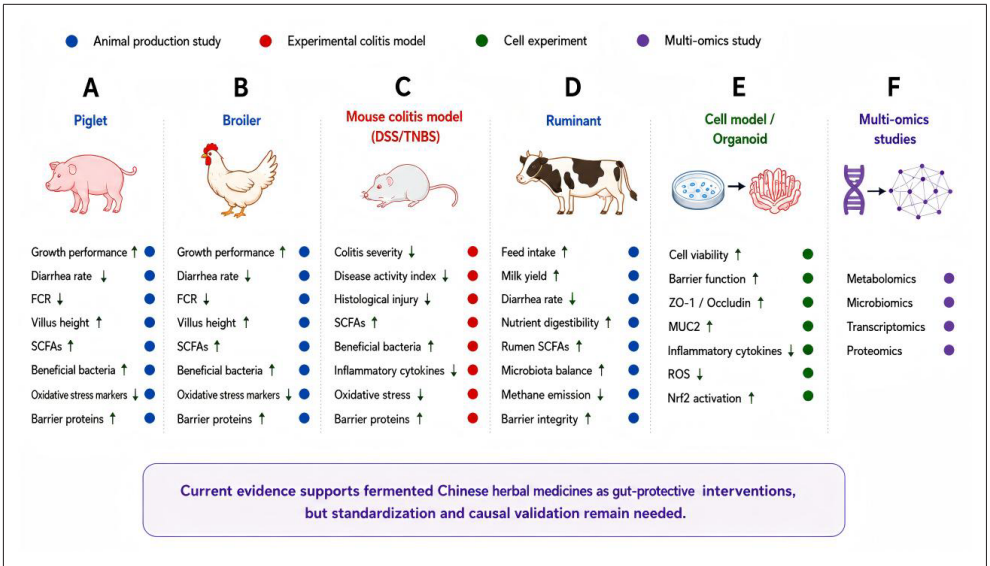

Fig 5. Overview of evidence supporting the gut-protective effects of fermented Chinese herbal medicines. **(A)** Studies in piglets have shown that fermented Chinese herbal medicines can improve growth performance, reduce the incidence of diarrhoea and the feed-to-meat ratio (FCR), increase villus height and SCFA levels, promote the proliferation of beneficial bacteria, alleviate oxidative stress and improve intestinal barrier function; **(B)** Studies in broiler chickens have shown that fermented Chinese herbal medicines can improve production performance and intestinal morphology, increase SCFA levels and the abundance of beneficial bacteria, alleviate oxidative stress and enhance barrier integrity; **(C)** Studies in DSS/TNBS-induced colitis models in mice have found that fermented Chinese herbal medicines can reduce disease severity and tissue damage, increase SCFA levels and the abundance of beneficial bacteria, enhance the expression of barrier proteins, and inhibit inflammation and oxidative stress; **(D)** Studies in ruminants have shown that fermented Chinese herbal medicines can increase feed intake, milk yield and nutrient digestibility, improve ruminal fermentation and microbial balance, and reduce methane emissions; **(E)** Cell and organoid studies have shown that fermentation metabolites can enhance cell viability, strengthen epithelial barrier function, promote the expression of tight junction proteins and MUC2, reduce levels of inflammatory cytokines and ROS, and activate antioxidant pathways such as Nrf2; **(F)** Multi-omics studies, including metabolomics, microbiomics, transcriptomics and proteomics, have further elucidated the molecular mechanisms by which fermented Chinese herbal medicines regulate the gut microbiota, host metabolism and immune responses

unambiguous strain identification, preferably based on whole-genome sequencing with deposition in recognised culture collections; (ii) fully defined fermentation parameters, including substrate composition, inoculum size, temperature, pH, moisture, oxygen regime and duration; (iii) chemical standardisation based on marker compounds or quality markers (Q-markers) linked to the intended bioactivity [109]; and (iv) untargeted metabolomic fingerprinting to confirm batch consistency and product stability during storage [32,33]. Only with such controls can dose-response relationships be compared meaningfully across studies and preparations.

From a commercial perspective, the doses used in experimental studies warrant critical appraisal. Inclusion levels reported in piglet trials (for example, 0.6% dietary inclusion of a fermented herbal formulation [4]) are within ranges considered economically feasible for commercial feed formulation, whereas high-dose extract regimens or short-term intensive administration may be impractical under field conditions [88]. Cost-effectiveness will depend on substrate availability, fermentation scalability and product stability; solid-state fermentation of agro-industrial residues offers a low-cost production platform in this regard [27,30]. Expressing doses in terms of defined marker-compound content rather than raw herb equivalents would further facilitate commercial translation and regulatory evaluation.

Conclusion

Existing research supports the intestinal anti-inflammatory potential of fermented Chinese herbal medicines, though evidence quality varies considerably. Early studies demonstrate protective effects against LPS- and neomycin-induced intestinal injury, yet lack in-depth analysis of ingredient biotransformation and microbiota-mediated mechanisms [49]. Trials conducted in production animals fit practical breeding scenarios, but complex dietary and environmental confounding factors restrict the interpretation of causal relationship [84]. Although murine DSS colitis models enable relatively complete mechanistic exploration, findings cannot be reliably extrapolated to porcine post-weaning diarrhoea due to interspecies difference [51].

Studies on flavonoid glycoside hydrolysis and fermentation-induced phenolic remodelling provide representative

evidence for active ingredient biotransformation [41,43]. Nevertheless, numerous animal experiments lack quantitative compositional comparisons pre- and post-fermentation, obstructing the identification of truly bioactive compounds.

Mechanistically, most investigations converge on the "microbiota-barrier-inflammation" axis; however, widespread issues of strong correlation without confirmed causality remain unresolved. Alterations in gut microbiota may occur either prior to or secondary to inflammation, and elevated SCFA concentrations could exert direct barrier protection or merely accompany the enrichment of beneficial commensals. Rigorous validation via faecal microbiota transplantation, metabolite supplementation and receptor blockade experiments is required to establish definitive causal links [45]. Future high-quality research should adopt multi-omics screening to uncover candidate pathways, followed by targeted functional verification.

Industrial standardisation constitutes a major bottleneck. Large discrepancies in starter strains, substrate proportion, fermentation humidity, temperature, duration and drying protocols hinder cross-study comparison of product composition and biological efficacy [24]. It is urgent to build a systematic quality evaluation system covering raw material fingerprints, fermentation termination indicators, quantitative detection of active ingredients and safety assessment.

Future investigations should develop targeted fermentation strategies within the "strain-substrate-metabolite-host" conceptual framework. Researchers can screen functional strains capable of transforming specific herbal components and select tailored fermented products according to enteritis phenotypes and baseline intestinal microbiota profiles [101]. Microbial fermentation improves the bioaccessibility of herbal constituents via polysaccharide degradation, glycoside hydrolysis and phenolic compound release. The resulting fermented preparations regulate gut microbiota, reinforce intestinal barrier integrity, inhibit NF-κB/NLRP3 signalling and mitigate oxidative stress. To fully exploit their application prospects in livestock production, the field needs to address inconsistent fermentation protocols, ambiguous strain selection criteria, insufficient evidence of component transformation, inadequate mechanistic validation and scarce large-scale field trials. Ultimately, a complete and reproducible evidence chain spanning strain, bioactive components, metabolites, gut microbiota, host responses and *in vivo* efficacy should be established. In summary, the most reliable effects of fermented Chinese herbal medicine in production animals are the combinatorial biotransformation of herbal components and the promotion of growth performance, along with mechanisms of barrier protection, anti-inflammation, and microbiota regulation. Although biologically plausible and increasingly supported by evidence, these effects are still at an early stage and require verification in target animals through standardized and controllable dosage trials, while also clearly addressing issues such as safety, standardization, and commercial feasibility.

Declarations

Availability of Data and Materials: As this is a review article, no original datasets were generated or analyzed. All information discussed in this review is provided within the manuscript and its cited references.

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