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REVIEW

Fermentation-Induced Changes in Phytochemical Composition and Pharmacological Activities of *Zingiberaceae* Plants: Insight from in vitro and in vivo Studies

Suci Fitriani Sammulia[1–3,*], Suhaera Suhaera[1,3,*], Deshanda Kurniawan Prayoga[1,4,*], Pitriani Pitriani[5,*], Zelika Mega Ramadhania[3,*], Adryan Fristiohady[6,*], Tiana Milanda[3,*]

[1]Doctoral Program in Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, West Java, Indonesia; [2]Department of Pharmacy, Faculty of Health Sciences, Institut Kesehatan Mitra Bunda, Batam, Riau Islands, Indonesia; [3]Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia; [4]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, West Java, Indonesia; [5]Departement of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, West Java, Indonesia; [6]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Halu Oleo, Kendari, Southeast Sulawesi, Indonesia

*These authors contributed equally to this work

Correspondence: Tiana Milanda, Department of Biological Pharmacy, Faculty of Pharmacy, Padjadjaran University, Sumedang, West Java, 46363, Indonesia, Tel +6222-84288888 ext 3510, Email tiana.milanda@unpad.ac.id

Abstract: The *Zingiberaceae* family has long been used in traditional medicine due to its rich array of secondary metabolites. However, its low bioavailability, limited stability in its native form, degradation during digestion, and poor solubility in water all restrict its absorption in the human body. Fermentation represents an effective biotechnological method for modifying the phytochemical composition and potentially enhancing its pharmacological effects. This study aims to explore the impact of fermentation on *Zingiberaceae*, focusing on the alteration of phytochemical profiles and the enhancement of pharmacological activities. Articles were sourced from the Scopus and PubMed databases and filtered for publications between 2015 and 2025; there were 2 articles that were electronically removed before screening due to duplication, yielding 62 articles. These articles were then further screened based on titles, abstracts, and full texts, resulting in five relevant studies. Fermentation was found to improve the phytochemical profile, influenced by the microbial strains used and the physicochemical properties of the phytochemicals. The fermentation process enhanced the stability of compounds, such as converting 6-gingerol to 6-shogaol and transforming glycosides into aglycones, which are more easily absorbed by the body. Additionally, fermentation increased phenolic and flavonoid content, accompanied by enhanced antioxidant and anti-inflammatory activities. Pharmacologically, in vitro studies showed that fermented extracts modulate cytokine signaling pathways in immune cells while enhancing anti-aging properties and skin barrier protection. Meanwhile, in vivo studies demonstrated improvements in metabolic regulation and neuroprotective effects in cognitive disorders. Further mechanistic investigations are needed to clarify the pathways through which fermentation influences the behavior of phytoconstituents and their pharmacological performance. This review provides an overview of preclinical fermentation studies on *Zingiberaceae* plants, both in vitro and in vivo, with a focus on their phytochemical composition and effectiveness in enhancing pharmacological activity.

Keywords: fermentation, fermented plant-based, phytochemicals, pharmacology activity, *Zingiberaceae*

Introduction

The use of medicinal plants for the management of the various diseases has been practiced for centuries and is widely known as phytotherapy.[1] The therapeutic potential of medicinal plants is primarily attributed to their rich content of secondary metabolites, commonly referred to as phytochemicals, which are naturally synthesized and continuously replenished in plant tissues.[2–5] These bioactive compounds were abundantly present in different plant parts, including

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seeds, barks, roots, leaves, flowers, and fruits. In plants, phytoconstituents also function as protective agents against environmental stressors and pathogenic microorganisms.[5,6]

Among medicinal plant groups, the *Zingiberaceae* family is recognized as one of the most important sources of pharmacologically active compounds. *Zingiberaceae* is a monocotyledonous plant family predominantly distributed across South and Southeast Asia, including Indonesia, Singapore, Malaysia, comprising approximately 53 genera and more than 1300 species.[7,8] Some well-known plants in the *Zingiberaceae* family, such as *Zingiber officinale, Alpinia galanga, Curcuma longa, Kaempferia galanga, Curcuma xanthorrhiza*, and *Amomum villosum*, have potential pharmacological effects. Plants of this family are extensively used in the food industry, particularly as flavoring agents and spices in culinary applications. Beyond their role in food, *Zingiberaceae* plants have attracted considerable attention due to their medicinal properties.[9–11] Numerous studies have reported their diverse biological activities, including antioxidant,[12–14] anti-inflammatory,[15–17] anti-proliferative,[18,19] antiplatelet,[20,21] anti-ulcer,[22,23] anticonvulsive,[24,25] and analgesic effects.[26] As a result, these plants are widely incorporated into traditional medicine systems as well as pharmaceutical products. Currently, there have been several studies in comprehensive metabolomics profiling of the chemical composition and metabolite variability of *Zingiberaceae* plants. For instance, metabolite profiling studies across multiple *Zingiberaceae* species have identified a broad spectrum of compounds, including curcumin, gingerol, galangin, organic acids, flavonoids, and diarylheptanoids.[27–29]

Although *Zingiberaceae* plants exhibit considerable pharmacological potential, the biological effectiveness of their phytoconstituents is constrained by several inherent limitations. These include low bioavailability and limited stability in their native forms, degradation during digestion, and poor aqueous solubility, all of which restrict efficient absorption in the human body.[30–32] Many key bioactive compounds from *Zingiberaceae*, such as curcumin and 6-gingerol, display poor water solubility and are susceptible to degradation when exposed to heat, oxygen, or light.[33–35] In addition, conventional extraction techniques frequently result in partial degradation or incomplete liberation of bioactive compounds from plant cell walls.[36–38] Even when successfully extracted, these compounds often exhibit low intestinal absorption and minimal systemic availability. For example, the oral bioavailability of curcumin in humans has been reported to be less than 1%.[39–42] These limitations highlight the need for processing strategies that can modify phytochemical composition while preserving or enhancing biological activity.

Fermentation represents a viable approach to addressing these limitations; it is a biotechnological process that employs microorganisms classified as Generally Recognized as Safe (GRAS) to modify the chemical structure of natural compounds into forms with enhanced biological activity, thereby potentially improving pharmacological effects.[39–42] Fermentation processes in plants can enhance the pharmacological activity of bioactive compounds through enzymatic mechanisms involving *β-glucosidase*. This enzyme plays a critical role in hydrolyzing glycoside bonds between sugar moieties and aglycones in plant glycosides. During fermentation, microorganisms such as *Aspergillus spp., Saccharomyces spp*., and lactic acid bacteria produce *β-glucosidase*, which catalyzes the conversion of glycosides into free aglycones and simple sugars. This biotransformation leads to an increase in the lipophilicity of the resulting compounds, thereby facilitating their cellular uptake and improving their bioavailability. Consequently, the release of aglycone forms is associated with enhanced pharmacological activities, including antioxidant, antimicrobial, anti-inflammatory, and immunomodulatory effects. Through microbial and enzymatic transformations, fermentation can overcome key challenges in the development of plant-based therapeutics, particularly by converting glycosylated compounds with low bioavailability and poor absorption into aglycone forms that are more readily absorbed by the human body.[43–45] In addition, fermentation has been shown to enhance the absorption and systemic distribution of bioactive compounds. Evidence supporting these effects has been reported for members of the *Zingiberaceae* family. For example, fermentation of *Curcuma longa* using *Lactobacillus rhamnosus* FN7 resulted in a significant increasing in phenolic and flavonoid contents, accompanied by enhanced antioxidant and anti-inflammatory activities.[46–48] Although research on fermented *Zingiberaceae* has increased in recent years, existing reviews largely emphasize fermentation techniques and microbial strain selection, with limited integration of phytoconstituents changes and functional bioactivity outcomes.

Taking this all into consideration, this review aims to provide an examine the effects of fermentation on phytochemical composition and associated pharmacological activities of plants belonging to the *Zingiberaceae* family. The review

synthesizes current evidence on fermentation-driven qualitative and quantitiative changes in bioactive compounds and evaluates how these compositional modifications are associated with biological compounds based on preclinical evidence, in vitro and in vivo studies. Overall, this review provides a structured and critical synthesis of existing findings and highlight research gaps relevant to the development of fermented *Zingiberaceae*-based plants, with particular emphasis on underlying mechanisms, phytoconstituent alterations, cellular-level evaluations using cell lines or assay kits, and pharmacological assesments in animal models.

Methods

Search Strategy

The search strategy was initially concentrated on articles published between 2015 and 2025. References were obtained from Scopus and PubMed Databases using keywords such as "Zingiberaceae," "Fermentation," and "Pharmacological Activity." The related terms and alternative phrases pertinent to the research topics were also included. Throughout the search process, synonyms and related terminology were employed interchangeably. Boolean operators like "AND" and "OR" were utilized to refine the search results, facilitating the inclusion or exclusion of specific terms. The search continued until August 2025, following a combination of medical subject headings (MeSH terms). The documents selected for review adhered to the inclusion criteria, focusing specifically on the fermentation of *Zingiberaceae* and its enhancement of pharmacological activity, rather than on general biological effects. In total, 5 articles were chosen for in-depth examination.

Data Selection and Collection Process

The study selection process was conducted systematically in accordance with the PRISMA 2020 guidelines to ensure transparency and reproducibility. Initially, a total of 64 records were identified through a comprehensive search of electronic database (Pubmed and Scopus). After removing 2 duplicate records, 62 articles remained for the initial screening stage. During the initial screening stage, titles and abstracts were screened using the Rayyan.ai (https://new.rayyan.ai/) to identify potentially relevant articles. Studies that met the initial criteria proceeded to full-text evaluation.

To be eligible, articles needed to be reported about the fermentation methods and their influence in phytoconstituents, with a specific focus on fermentation methods, including the microorganisms employed, fermentation conditions, and quantitative analysis of phytoconstituents, as well as report preclinical findings derived from cell-line experiments, assay-based evaluations, and animal models was considered. Articles were excluded if they were reviews, commentaries, or did not primarily focus on the specific species of interest. To evaluate the quality of the included studies and address variations in evidence strength, a structured quality assessment was performed. Studies were evaluated based on the transparency of their fermentation parameters. Data from the selected studies were manually retrieved and systematically extracted, covering a variety of study designs. These included analyses of phytoconstituent profiles based on these microorganisms used and fermentation conditions, with comparisons of phytochemical levels before and after fermentation. For in vitro investigations, extracted information included the type of cell lines employed, induction methods, and exposure duration. For in vivo studies, relevant data such as animal models, induction protocols, use of negative and positive controls, and study duration in weeks were recorded. Based on these inclusion criteria, a total of 5 articles were selected for detailed analysis (Figure 1).

Data Synthesis

Given the considerable variability across the studies and the differing outcome measures, a systematic synthesis of the evidence was performed. The findings were summarized qualitatively and organized thematically based on the reported results. To provide comprehensive context and address any gaps in the literature, this synthesis includes detailed sections on the species-specificity of microbial species that modulate phytoconstituents during fermentation. This thorough approach serves as a valuable resource for researchers, integrating biological context with an extensive review of the latest evidence.

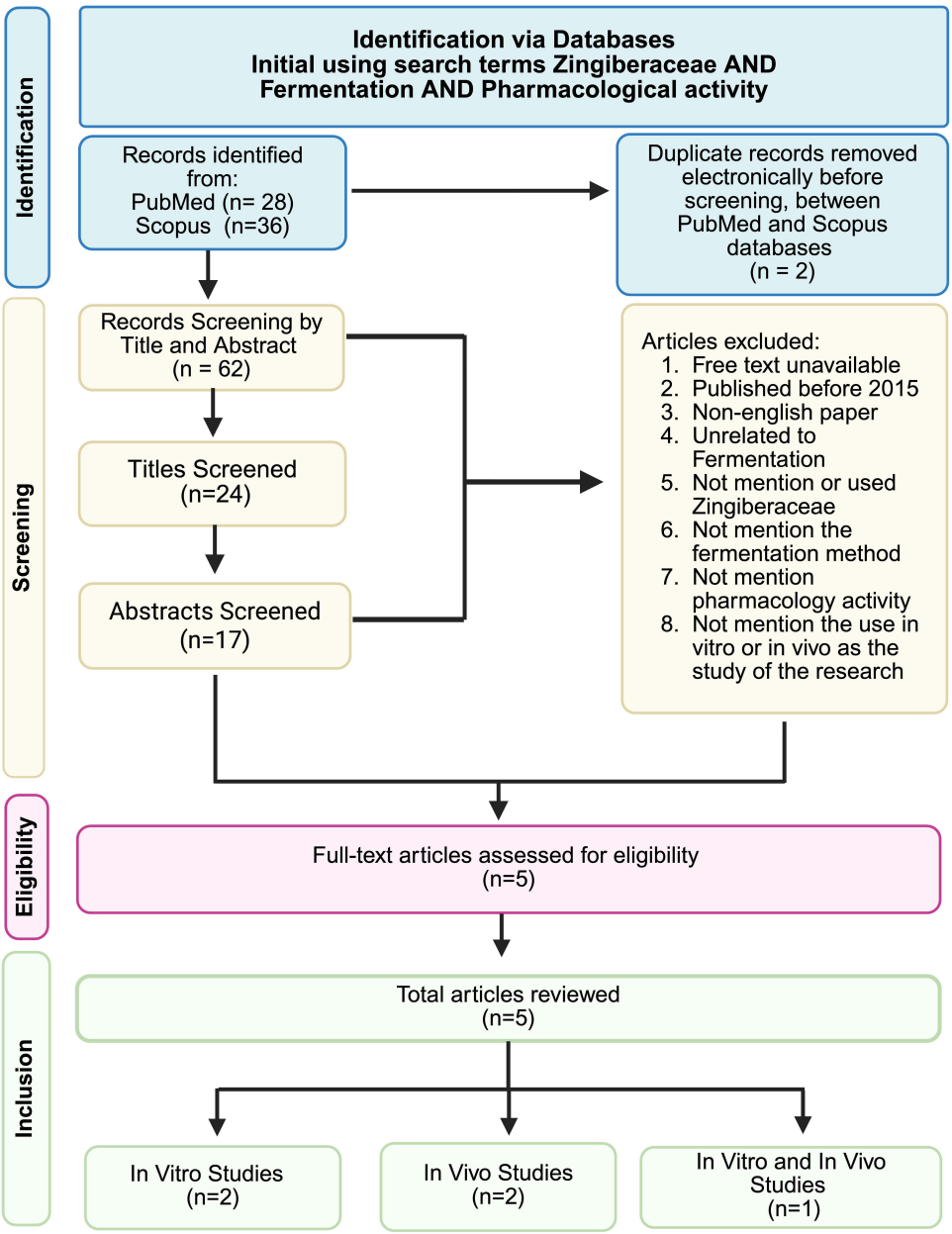

Figure 1 The study design of the article review.

Characteristics of Included Studies

The literature search conducted across two selected databases identified a total of 64 records. Duplicate records (n=2) were removed electronically, leaving 62 articles for screening. Titles and abstracts were screened for relevance using Rayyan.ai, resulting in 17 articles selected for full-text assessment. After detailed assessment, 5 studies met the eligibility criteria and were included in the final analysis. The study selection workflow is illustrated in Figure 1, which outlines the stages of identification, screening, eligibility, assessment, and final inclusion in accordance with the Standard PRISMA-based selection process. Key characteristics of included studies were systematically extracted, with particular attention to fermented plant-based interventions and their mechanisms influencing the upregulation or downregulation of phytoconstituent levels. The selected studies were categorized into two main groups, in vitro and in vivo investigations, to allow structured evaluation of evidence across experimental and translational contexts. For each study, descriptive information was recorded, including study design, biological model or population, intervention and induction methods, primary

outcomes assessed. These outcomes included biomarkers such as pro-inflammatory gene expression levels, including Interleukin-6 (*IL-6*), Tumor Necrosis Factor–alpha (*TNF-α*). Additional literature was consulted to support contextual interpretation and discussion, particularly regarding mechanisms affecting phytoconstituent levels and associated pharmacological enhancement. These supplementary sources were used solely for contextual support and were not included in the PRISMA flow diagram.

Results

Fermentation functions as an effective bioprocess capable of modifying the phytochemical composition of medicinal plants, particularly those belonging to the *Zingiberaceae* family, with consequent effects on their pharmacological activity. The collective evidence analyzed indicates that fermentation using specific microorganisms produce both qualitative and quantitative alterations in phytoconstituents of *Zingiberaceae* plants. These compositional changes are consistently associated with measurable effects on bioactivity, bioavailability, and therapeutic applicability, as observed across in vitro and in vivo experimental models. However, the direction of these changes varies considerable depending on the plant species, the microbial strains employed, and the specific fermentation conditions applied, highlighting the importance of controlled and species fermentation strategies. Across the literature studies, 5 articles were included. However, 2 article discussed in vitro studies, 2 articles discussed in vivo studies, and 1 article discussed both preclinical studies, including in vitro and in vivo. Across the included studies, fermentation was found to modulate phytoconstituent levels in *Zingiberaceae* plants, resulting in both upregulation and downregulation-specific compounds while maintaining or enhancing anti-inflammatory pharmacological activity.

Fermentation-Induced Modulation of Phytoconstituents in Zingiberaceae Plants

Fermentation is a biotechnological process used to modify the content and structure of bioactive compounds in natural materials, including flavonoids. This process involves the use of specific microorganisms, which enhances the bioavailability and pharmacological activity of flavonoid compounds.[49–52] Fermentation can convert glycosides into aglycones, which possess higher bioavailability. Several studies have demonstrated that flavonoid compounds are more stable and bioavailable after fermentation compared to their pre-fermentation state.[53–55]

Fermentation can quantitatively alter the phytoconstituents in the *Zingiberaceae* family, influenced by the type of fermentation and the microorganisms used during fermentation, as well as the fermentation conditions, such as temperature, pH, duration, and media composition.[53,56,57] Solid-state fermentation (SSF) using *Lactobacillus plantarum* (KCTC 3108, FLP8) on *Zingiberaceae officinale* showed that 6-gingerol and 6-shogaol remained unchanged after 48 hours of fermentation, indicating that both compounds are stable under these fermentation conditions. However, when a different strain of Lactobacillus plantarum (KCL005, FLP9) was used with a shorter fermentation duration of 24 hours, a significant increase in 6-gingerol and 6-shogaol was observed before and after fermentation.[58–61] This could be attributed to SSF providing a controlled enzymatic environment with low air activity, leading to the degradation of sensitive phenolic compounds while supporting partial biotransformation reactions that can modify the structure of specific compounds without damaging their core molecular structure.[62–64] The difference in strains has a greater impact on biotransformation compared to the plant species itself. Therefore, it can be concluded that SSF is suitable for modifying target bioactive compounds while maintaining the stability of their core structure, thereby yielding more effective and safer compounds for clinical applications.[65]

Other studies have demonstrated that *Curcuma longa*, containing the bioactive compound curcumin, exhibits antioxidant and anti-inflammatory activities. This study utilized yeast extract and ethanol for fermentation at 37°C for 24 hours, after which the curcumin content in the fermented *Curcuma longa* was measured.[65] The curcumin content after fermentation showed a decrease, which may be due to the degradation of curcumin during fermentation. This suggests that microbial activity can break down the compound into other bioactive metabolites, a phenomenon also observed with the compound demethoxycurcumin.[66] However, no significant changes were observed in bisdemethoxycurcumin after fermentation, indicating that this compound is stable during the fermentation process. The fermentation in this study also released compounds bound to the cellular matrix, as well as non-chromophoric precursors, which, initially undetectable by analytical methods, underwent changes that allowed them to be detected using more sensitive analyses.[66] Therefore, it

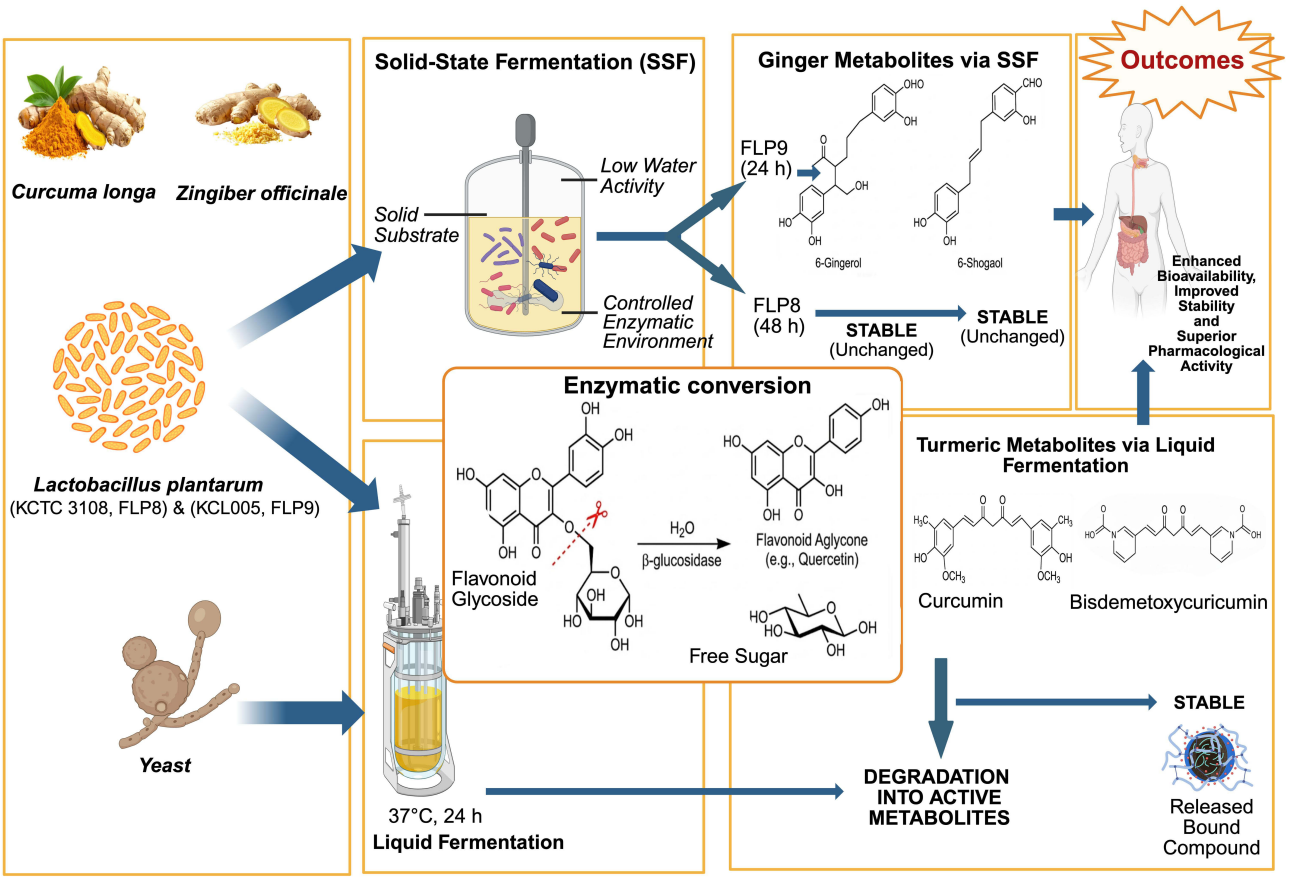

Figure 2 Mechanisms of fermentation-induced phytochemical transformation in *Zingiberaceae* plants.
Notes: Aglycone: the non-sugar compound remaining after replacement of the glycosyl group from a glycoside.6-shogaol: a potent dehydrated derivative of 6-gingerol produced during fermentation. FLP8, *Lactobacillus plantarum* strain KCTC 3108. FLP9, *Lactobacillus plantarum* strain KCL005.

can be concluded that fermentation can facilitate chemical changes and enhance the bioactivity of compounds in *Curcuma longa*, thereby strengthening its therapeutic potential and making it suitable for drug development applications (Figure 2).

Overall, the reviewed evidence demonstrates that fermentation acts as a decisive modulator of phytoconstituents profiles in *Zingiberaceae* plants by altering both compound abundance and structural form (Table 1). Although the underlying molecular mechanisms were not directly investigated in most studies, the observed-changes in phytochemical profiles and biological activity suggest that fermentation-related biotransformation plays an important role in improving the functional properties of *Zingiberaceae*-derived compounds. Further mechanistic investigations are required to clarify the pathways through which fermentation influences phytoconstituent behavior and pharmacological performance.

Species-Specific Microbial Modulation of Phytoconstituents

The fermentation of plants within the *Zingiberaceae* family is increasingly recognized as a biochemical process governed by microbial species-specificity. Each microbial species introduces a distinct enzymatic and metabolic capacity that shapes the conversion, upregulation and stabilization of plant-derived bioactive compounds.[70–72] These phytoconstituents, primarily curcuminoids, gingerols, shogaols, and phenolic derivatives, undergo targeted transformations depending on the metabolic repertoire of the fermenting microbe, resulting in enhanced bioactivity and functional diversity.

Studies combining microbiome and metabolomic analyses reveal that microbial species interact synergistically to drive phytochemical enhancement during fermentation. For example, *Bacillus coagulans* and lactic acid bacteria such as *Leuconostoc* and *Pediococcus* were shown to upregulate β-glucosidase activity, hydrolyzing glycosidic bonds in flavonoid conjugates and thereby increasing free aglycone levels such as quercetin and caffeic acid.[73–75] This enzymatic

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Table 1 Phytochemical Profile and Biological Potential of Fermented Medicinal Plants

No	Plant species, Collection Locale/ Year	Plant Part, Fermentation or Extraction Method (Solvent-Used)	Type of Fermentation		Specific Phytoconstituents	Quantification of Phytoconstituents		In Vitro Evidence (Cell Type, Inducement Method, Exposure time)	In Vivo Evidence (Animal Used in the Preclinical Study, Inducement Method, Control (Negative and Positive), Duration (Weeks)	Results	Ref
			Microorganism Employed	Fermentation Conditions		Before	After				
1	*Aframomum angustifolium* (Sonn). K. Schum. Vohimana, Madagascar / Harvested in 2020.	Dried Seeds, Aqueous-based bio-fermentation (Solvent: Distilled water/ Culture medium).	Microbial Consortium S60: Saccharomyces cerevisiae, Lactiplantibacillus plantarum, and Leuconostoc mesenteroides	The consortium was pre-incubated in a medium containing water, sugar, and black tea infusion for 3 to 4 days at 26°C. Subsequently, ground Aframomum angustifolium seeds were added to the mixture to initiate the fermentation process for a period of 10 days	Gluconic acid, quinic acid, succinic acid	N.D	Gluconic acid 1), quinic acid 2), and succinic acid 6), with concentrations of about 2%, 1%, and 0.5%, respectively. Small amounts of malic acid 3), lactic acid 4), and citric acid 5) at about 0.1% were also measured.	Normal Human Epidermal Keratinocytes (NHEK), Normal Human Dermal Fibroblasts (NHDF), and 3D Bioprinted Skin Equivalents.H2O2-induced oxidative stress (for senescence) and calcium-induced differentiation.24–48 hours (monolayer cultures); 21 days (3D skin equivalent maturation).	Not evaluated	Significant upregulation of barrier markers (Filaggrin, Loricrin) and dermal proteins (Collagen I, III). Reduction in senescence markers (p16, p21) and MMP-1.	[67]

(*Continued*)

Table 1 (Continued).

No	Plant species, Collection Locale/ Year	Plant Part, Fermentation or Extraction Method (Solvent-Used)	Type of Fermentation		Specific Phytoconstituents	Quantification of Phytoconstituents		In Vitro Evidence (Cell Type, Inducement Method, Exposure time)	In Vivo Evidence (Animal Used in the Preclinical Study, Inducement Method, Control (Negative and Positive), Duration (Weeks)	Results	Ref
			Microorganism Employed	Fermentation Conditions		Before	After				
2	*Amomum xanthioides*, Korea, (N/A)	N/A, Solid state-fermentation using MRS Medium (Ethyl Alcohol 30%)	Lactobacillus casei	Inoculated at 2% (v/v) and incubated at 30°C for one week	Procyanidin B2	5.07 μg/mg	N.D	Not evaluated	In vivo on male mice (Mus musculus with Strain C57BL/6J), age 6 week, weighing 19–21 g (n=40).	Treatment with AX and LAX reduced liver and fat mass in HFD-fed mice, with LAX showing a greater effect. Both treatments reversed liver color changes, increased liver weight, and fat mass caused by HFD, while lowering lipid synthesis proteins (SREBP-1, GPAM) and increasing lipolysis proteins (PPAR-α). LAX also normalized pAMPK-α levels. Both treatments reduced lipid droplet accumulation, inflammation, and hepatocyte ballooning, while decreasing AST, ALT, and inflammatory cytokines (TNF-α, IL-6, IL-1β). Additionally, AX and LAX alleviated oxidative stress and normalized ER stress-related mRNA expression, with LAX being more effective. These results suggest LAX is more effective than AX in improving liver function and reducing oxidative stress, making it a promising therapeutic for HFD-induced metabolic issues.	[68]
					Catechin	N.D	14.42 μg/mg				

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									HFD-induced Obseity (60% kcal% fat) Via Oral Ingestion for 4 weeks.		
					Flavonoids	6.6 mgGAE/g	76.2 mgGAE/g				
									HFD induced as a negative control and Metformin at dose 100 mg/kg/day) as positive control. Duration in 10 weeks		
					Phenolics	21.6 mgGAE/g	142.4 mgGAE/g				
3	*Curcuma Longa*, Taiwan, N/A	Turmeric Powder, Solid state-fermentation using MRS Medium (N/A)	Lactobacilus Paracasei	Inoculated at 2% (v/v), and incubated at 37°C for 20 hours.	Curcumin	5627.8 ug/g	3849.2 ug/g	Not evaluated	In vivo on male mice (Mus musculus with Strain C57BL/6J), age 5–8 weeks, weighing 21–23 g (n=40).	FT supplementation in HFD-fed mice for 16 weeks delayed body weight gain, with the HFD + FT group gaining 9.96 ± 0.58 g compared to the HFD group's 11.68 ± 0.63 g. There were no significant differences in food intake across groups. Serum AST and ALT levels showed no toxicity from UT or FT. Supplementation with FT led to significant reductions in total cholesterol (TC) and LDL-C compared to HFD, though HDL-C remained unchanged. FT also reduced hepatic lipid accumulation, liver weight, and visceral adipose tissue size, with smaller adipocytes in FT and UT groups. FT reduced the expression of PPAR-γ, C/EBPβ, and FASN proteins, while SIRT1 expression was increased. FT also enhanced liver fatty acid β-oxidation by upregulating pAMPK/AMPK, PPARα, and PGC-1α. In the OGTT, FT improved glucose tolerance and reduced insulin resistance (HOMA-IR). FT supplementation elevated PI3K/Akt signaling and reduced inflammatory cytokines in hepatic and adipose tissues.	[67]

(*Continued*)

Table 1 (Continued).

No	Plant species, Collection Locale/ Year	Plant Part, Fermentation or Extraction Method (Solvent-Used)	Type of Fermentation		Specific Phytoconstituents	Quantification of Phytoconstituents		In Vitro Evidence (Cell Type, Inducement Method, Exposure time)	In Vivo Evidence (Animal Used in the Preclinical Study, Inducement Method, Control (Negative and Positive), Duration (Weeks)	Results	Ref
			Microorganism Employed	Fermentation Conditions		Before	After				
					Demethoxycurcumin	1886.4 ug/g	1355.6 ug/g				
									HFD-induced Obesity (50% energy from fat in diet using the Purina 5001 diet) via Oral Ingestion.		
					Bisdemethoxycurcumin	1340.4 ug/g	970.8 ug/g				
									HFD induced as a negative control.		
									Duration in 16 weeks		

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4	*Curcuma longa*, Korea, N/A	Turmeric Powder, Solid-State fermentation using 2% yeast extract (70% ethanol)	Lactobacillus Plantarum K154	Solid-state, inoculated at 5% (v/v), and incubated 30°C for 70 hours.	Curcumin	N.D	10.37 ± 0.57 (μg/mg)	BV2 Murine microglial cells stimulated by LPS for 24 hours	In vivo on Male mice (*Mus musculus* with strain ICR/CD-1), weighinging 23–25 g (n=48).	In vitro: Fermented curcuma longa at dose 10–150 μg/mL was showed non cytotoxicity effects towards BV2 cells ($p>0.005$), similar to curcumin (positive control). At dose 50 μg/mL) significantly suppressed NO production by 91.64% compared to LPS-only stimulation, while curcumin reduced NO by 76.9%. FCL also inhibited PGE2 production in a concentration-dependent manner ($P < 0.001$), and TNF-α levels were dose-dependently reduced, with 150 μg/mL leading to undetectable levels. Moreover, FCL reduced iNOS and COX-2 protein expression in a dose-dependent manner, particularly at concentrations over 50 μg/mL ($P < 0.05$).	[69]
					Demethoxycurcumin	N.D	1.68 ± 0.08 (μg/mg)		Scopolamine-induced memory deficit (1 mg/kg) via intraperitoneal.		
									Vehicle solution (10% Tween 80) as negative control, Donezepil at dose 5 mg/kg as positive control.		
					Bisdemethoxycurcumin	N.D	2.23 ± 0.22 (μg/mg)				
									Duration in 4 days		

(*Continued*)

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Table 1 (Continued).

No	Plant species, Collection Locale/ Year	Plant Part, Fermentation or Extraction Method (Solvent-Used)	Type of Fermentation		Specific Phytoconstituents	Quantification of Phytoconstituents		In Vitro Evidence (Cell Type, Inducement Method, Exposure time)	In Vivo Evidence (Animal Used in the Preclinical Study, Inducement Method, Control (Negative and Positive), Duration (Weeks)	Results	Ref
			Microorganism Employed	Fermentation Conditions		Before	After				
										In vivo: Treatment with FCL improved memory in scopolamine-induced amnesia mice, assessed through the step-through passive avoidance test and the Morris water maze. In the step-through test, FCL (100 and 200 mg/kg) significantly increased the retention time compared to scopolamine. Similarly, in the Morris water maze, FCL (50, 100, and 200 mg/kg) reduced escape latency and increased swimming time in the target quadrant, indicating improved spatial memory. AChE inhibition was identified as a mechanism underlying these effects, with FCL inhibiting AChE activity in a concentration-dependent manner (IC50 = 48.79 ± 5.46 μg/mL). FCL also enhanced pCREB and BDNF expression in the hippocampus, key molecules involved in memory formation. These findings suggest that FCL enhances memory via AChE inhibition and activation	

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5	*Zingiber Officinale*, Korea, N/A	Rhizome, Cold Water Extraction (Ice-Cold distilled water)	Lactobacillus Plantarum (KCTC 3108, FLP8)	Solid-state, inoculated at 1% (v/v), and incubated at 37°C for 48 hours.	6-Shogaol	10 mg/g	10 mg/g	RAW 264.7 murine macrophage cells stimulated by LPS and treated with fermented ZOE for 24 and 48 hours	Not evaluated	The fermented plants, FLP8 (48 h) and FLP9 (24 h), showed low cytotoxicity at 100 μg/mL and 200 μg/mL, and significantly reduced LPS-induced NO production at dose 200 μg/mL, with FLP8 showing a 91.77% decrease. Both FLP8 and FLP9 suppressed the expression of iNOS, TNF-α, IL-6, and IL-1β, with FLP8 demonstrating the strongest anti-inflammatory effect, proving more effective compared to unfermented ZOE.	[59]
			Lactobacillus Plantarum (KCL005, FLP9)	Solid-state, inoculated at 1% (v/v), and incubated at 37°C for 24 hours.	6-Shogaol	10 mg/g	16 mg/g				
			Lactobacillus Plantarum (KCL005, FLP9)	Solid-state, inoculated at 1% (v/v), and incubated at 37°C for 24 hours.	6-Shogaol	10 mg/g	16 mg/g				

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hydrolysis not only liberates bound phenolics but also enhances their solubility and antioxidant capacity, contributing to the improved biological activity observed in fermented *Zingiberaceae* extracts. Concurrently, fungal species such as *Rhizopus* spp. and *Aspergillus* spp. were consistently detected in fermentation systems exhibiting extensive substrate degradation. These fungi produced amylolytic and proteolytic enzymes that preceded bacterial metabolism and coincided with increased bioavailaibility of low-molecular-weight metabolites.[64,76–78]

Microbial species also differed in the metabolite classes enriched during fermentation, *Lactobacillus plantarum* was associated with increased amino acid and polyphenol levels, whereas *Lactobacillus buchneri* was linked to elevated volatile fatty acid production.[79–82] In addition, fermentation using *Lactobacillus brevis* and *Weissela cibaria* was associated with selective release of bound ferulic acid and lignans.[83–85] Overall, microbial species identity influenced both the direction and magnitude of phytochemical modulation during *Zingiberaceae* fermentation, resulting in distinct bioactive compound profile across fermentation systems.

In vitro Evidence

In vitro experimental studies commonly employ various cell-line models to investigate fermented natural products, including the murine macrophage cell line RAW 264.7, the murine microglial cell line BV-2, microbial consortia, and skin models such as Normal Human Epidermal Keratinocytes (*NHEK*), Normal Human Dermal Fibroblasts (*NHDF*), and 3D bioprinted skin equivalents.[58,69,86,87] These cell-line models are typically stimulated with lipopolysaccharide (LPS) to activate inflammatory responses, including the induction of inducible nitric oxide synthase (*iNOS*), tumor necrosis factor (*TNF-α*), interleukin (*IL-6*), and *IL-1β*.[67,88–90] In contrast, biological models of skin protection are often subjected to oxidative stress (H_2O_2 exposure and calcium-induced differentiation) to simulate cellular aging/senescence and disruption of the skin barrier.[87,91,92]

Recent studies on fermentation have demonstrated its potential to enhance the pharmacological activity of phytoconstituents compared with their non-fermented counterparts.[93,94] Kim et al[58] evaluated the anti-inflammatory activity of *Zingiber officinale* extract using LPS-stimulated murine RAW 264.7 macrophages. Fermented *Zingiber officinale* with *Lactobacillus plantarum* KCTC 3108 significantly reduced nitric oxide production by 91.77%, to 0.87 ± 0.12 μM, and fermentation with *L. plantarum* KCL005 resulted in a greater suppression of nitric oxide compared with the non-fermented extract. Gene-expression analyses further revealed that fermented *Zingiber officinale* markedly downregulated *iNOS, TNF-α, IL-6*, and *IL-1β*, while simultaneously increasing the concentrations of bioactive compounds, namely 6-gingerol and 6-shogaol. These findings are consistent with those reported by Eun et al,[86] in which fermented *Curcuma longa* exhibited superior neuroprotective activity compared with curcumin controls by suppressing NO production, inhibiting PGE_2 synthesis, and reducing iNOS and COX-2 expression in a dose-dependent manner Beyond its anti-inflammatory effects, fermented *Aframomum angustifolium* extract demonstrated significant tissue-repair mechanisms in skin cell models, showing substantial upregulation of key skin-barrier markers (filaggrin and loricrin), increased synthesis of dermal matrix proteins (collagen types I and III), and mitigation of aging through reductions in senescence markers (p16, p21) and Matrix Metalloproteinase-1 (MMP-1)[87] (Figure 3).

Overall, fermentation of plant extracts consistently enhances the pharmacological performance of phytoconstituents by modulating cytokine-signaling pathways in immune cells, while also improving anti-aging properties and skin-barrier protection. These observations indicate that the data presented in Table 1 provide a clear overview of in vitro studies demonstrating that fermented extracts modulate oxidative stress and inflammatory pathways, regulate nitric oxide signaling, and thus highlight their potential for the development of therapeutic agents for inflammation management and cosmetic applications.

In vivo Evidence

In vivo evidence indicates that fermentation consistently enhanced the pharmacological effects of *Zingiberaceae* phytoconstituents in metabolic, inflammatory, and cognitive impairment models. Fermented plant preparations suppressed pro-inflammatory gene expression and reduced oxidative stress in high-fat diet-induced models, while also improving cognitive performance in scopolamine-induced amnesia mice.[86,95,96] These findings indicate that

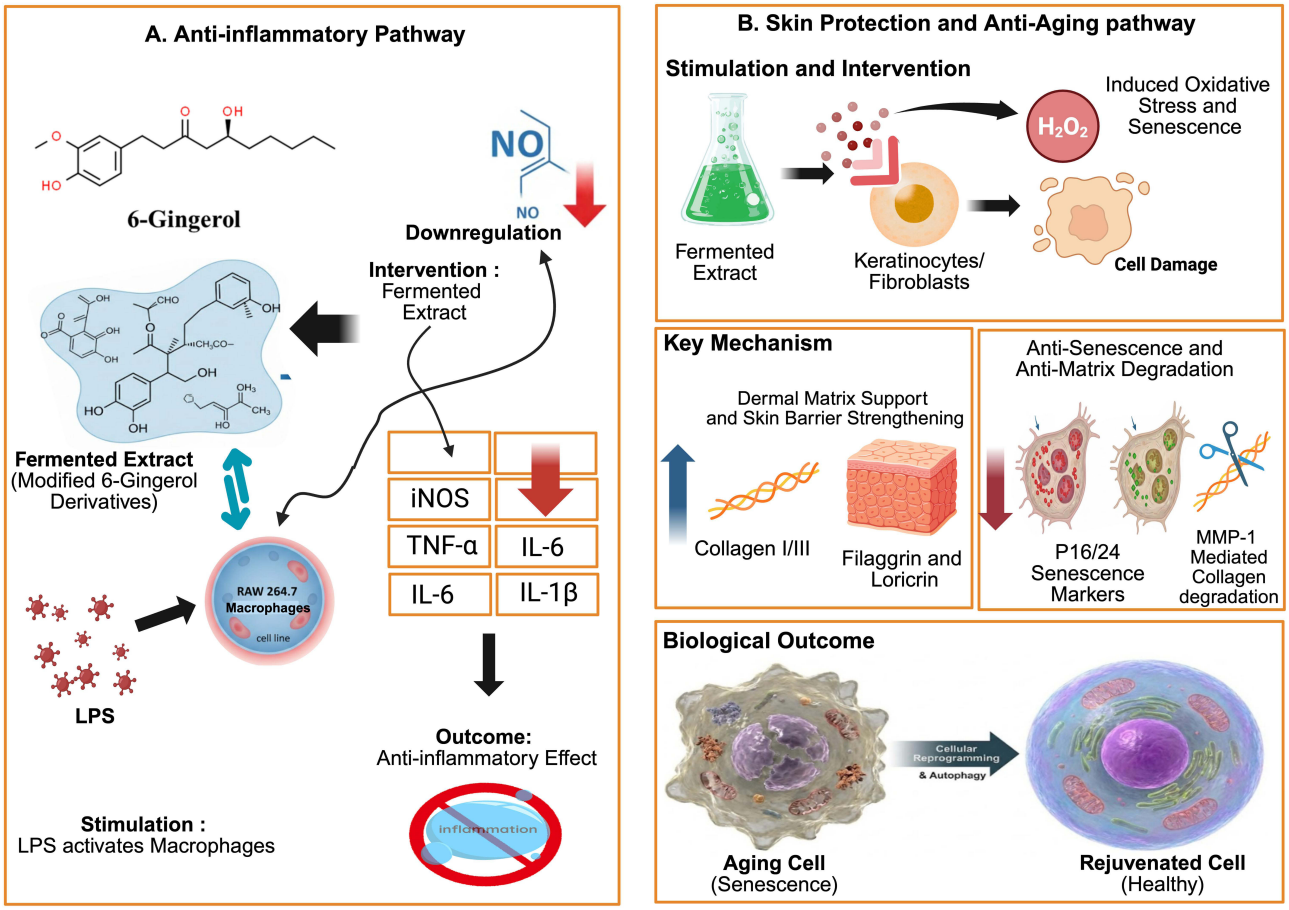

Figure 3 In vitro pharmacological mechanisms of fermented *Zingiberaceae* extracts. (**A**) Anti-inflammatory In LPS-stimulated RAW 264.7. (**B**) Skin protection and anti-aging pathway in Keratinocytes/Fibroblasts.

Notes: Blue upward arrows (↑) indicate stimulation, Red downward arrows (↓) indicate reductions or downregulation of inflammatory/aging markers.

Abbreviations: LPS, lipopolysaccharide; NO, nitric oxide; iNOS, inducible nitric oxide synthase; TNF-α, tumor necrosis factor-alpha; IL, interleukin; H_2O_2, hydrogen peroxide; MMP-1, matrix metalloproteinase-1.

fermentation-associated phytochemical modifications are functionally relevant in vivo, resulting in measurable biological outcomes.

Several studies demonstrated that microbial fermentation improved metabolic regulation by modulating lipid metabolism-related pathways. In high-fat diet-induced obese mice, fermented turmeric prepared using *Lactobacillus paracasei* showed greater efficacy than their unfermented counterparts, as evidenced by reduced expression of adipogenesis and lipogenesis markers such as Sterol Regulatory Element-Binding Protein 1c (*SREBP-1c*) and Fatty Acid Synthase (*FASN*), alongside increased Sirtuin 1 (*SIRT1*) expression in visceral adipose tissue and liver.[95–97] In parallel, fermented preparations enhanced hepatic fatty acid β-oxidation, reflected by increased levels of phosphorylated AMPK (*pAMPK*)/ AMP-activated protein kinase (*AMPK*), Peroxisome Proliferator Activated Receptor-Alpha (*PPARα*), and PPAR Gamma Coactivator-1 alpha (*PGC-1α*), suggesting protective effects against hepatic steatosis.[98–100] These effects were associated with activation of AMPK signaling and suppression of adipocyte differentiation-related transcription factors. Specific phytoconstituents generated or enriched during fermentation, including Calebin-A and bisacurone, were implicated in regulating lipogenic protein expression and promoting phosphorylation pathways linked to metabolic improvement.[101–104]

Furthermore, fermentation effects in cognitive impairment models also demonstrated neuroprotective effects. In scopolamine-induced amnesia mice, fermented extracts significantly increased hippocampal expression of phosphorylated CREB (*pCREB*) and Brain Derived Neurotropic Factor (*BDNF*), key molecular markers involved in memory formation.[86,105,106] *pCREB* and *BDNF* is a crucia; transcription factor that turns on specific genes involved in memory, learning, and cell survival by being activated by signals like Cyclic adenosine monophosphate (*cAMP*), calcium, and

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stress. Its presence indicates active gene expression, and its levels are studies in relation to brain disorders where it's often reduced in Alzheimer's disease.[107,108] Furthermore, Immunohistochemical and Western blot analyses revealed that fermented treatments reversed scopolamine-induced reduction in *pCREB* and *BDNF*-positive cells in the hippocampus. Behavioral assessments, including step-through passive avoidance and Morris water maze tests, further confirmed that fermented plant treatments significantly improved memory retention compared with scopolamine-treated controls and showed comparable effects to donezepil used as a positive control (Figure 4). [107,108]

Overall, the in vivo evidence indicates (Table 1) that fermentation of *Zingiberaceae* plants consistently enhances pharmacological activity through modulation of inflammatory responses, metabolic regulation and cognitive function. These findings support the relevance of fermentation as a bioprocess that improves the biological performance of plant-derived phytoconstituents and strengthens their translational potential in preclinical therapeutic applications.

Discussion

Fermentation has emerged as a biotechnological strategy capable of reshaping the phytochemical composition of medicinal plants, including members of *Zingiberaceae* family, with downstream effects on pharmacological activity.[46,109] Across the reviewed studies, fermentation consistently altered the qualitative and quantitative profiles of bioactive constituents, which was frequently accompanied by enhanced biological effects in both preclinical studies (i*n vitro* and in vivo models).[110–112] Importantly, these outcomes were not uniform, but were strongly influenced by plant species,

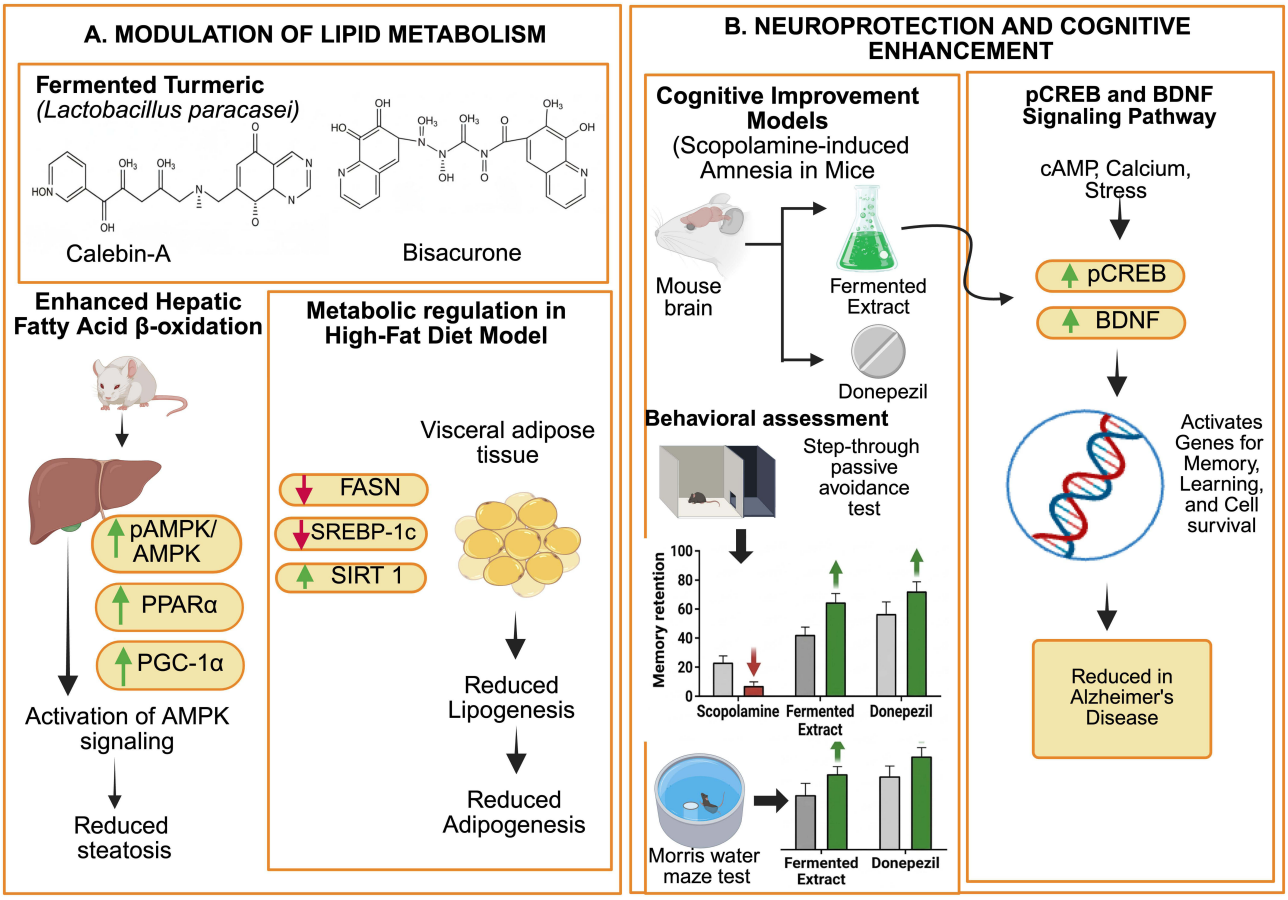

Figure 4 In vivo pharmacological effects of fermented *Zingiberaceae* extracts on metabolic and cognitive functions. (**A**) Mechanism; Modulation of Lipid Metabolism. (**B**) Mechanism: Neuroprotection and Cognitive Enhancement.

Notes: Green arrows upward (↑) indicate an increase or activation of the pathway. Red arrows downward (↓) indicate a decrease or inhibition of metabolic markers.

Abbreviations: AMPK, AMP-activated protein kinase; PPARα, peroxisome proliferator-activated receptor alpha; PGC-1α, PPAR Gamma Coactivator-1 alpha; FASN, fatty acid synthase; SREBP-1c, sterol regulatory element-binding protein 1c; SIRT1, sirtuin 1; pCREB, phospho-cAMP response element-binding protein; BDNF, brain-derived neurotrophic factor.

microbial strains, and fermentation parameters, indicating that fermentation acts as a context-dependent modulator rather than a universally enhancing process.[41,113–115]

Several studies reported an apparent contradiction, in which a quantitative reduction in certain phytoconstituents coincided with enhanced pharmacological activity. This phenomenon frequently ascribed to microbial enzyme-mediated biotransformation, specifically the hydrolysis of inactive glycosidic forms into more biologically active aglycones.[116–118] Fermentation might also help break down complex phytochemicals into smaller molecules, which could make it easier for cells to take them up and for tissues to absorb them.[68,119,120] From a conventional phytochemical perspective, reductions in total apparent compounds may be interpreted as a loss of therapeutic potential. However, the reviewed evidence suggests that biological activity is not solely determined by total compound concentration, but also by chemical form, molecular size and functional availability.[121,122]

Similar compositional shifts were observed in the fermentation of *A. xanthioides* using *Lactobacillus casei*, which resulted in increased total flavonoid and phenolic content alongside the loss of specific compounds such as procyanidin B2.[49,123,124] The increase in total phenolics was proposed to arise from the release of matrix-bound compounds or the generation of low molecular weight phenolics during microbial metabolism.[125–128] These compositional changes were associated with significant hepatoprotective effects in a rat model of non-alcoholic fatty liver disease. Although direct causal mechanisms were not fully elucidated, the findings indicate that fermentation can enhance the functional availability of bioactive constituents, thereby influencing systemic biological responses.[129–132]

Another study demonstrated that ginger (*Z. officinale*) fermented with *L. plantarum* bacteria leads to increased stability of 6-gingerol and 6-shogaol after the fermentation process. The bacteria produce enzymes that can remove a single water molecule (a dehydration process) from 6-gingerol, converting it into 6-shogaol. The compound 6-shogaol is more stable and exhibits significantly higher antioxidant activity compared to regular gingerol. It has been shown to enhance the immune cell (RAW 264.7 macrophage) ability to combat inflammation in vitro.[58,133–135] This study explains that ginger can act as an immunomodulator through the pro-inflammatory signaling pathways. Fermented ginger was found to inhibit Nitric Oxide (*NO*) production by more than 90% (a very strong effect) and reduce cytokine expression such as Tumor Necrosis Factor-α (*TNF-α), IL-6*, and *IL-1β*.[136–139] The study further indicates that the increased concentration of 6-shogaol works through dual inhibition of the Mitogen-Activated Protein Kinase (*MAPK*) pathway, specifically p44/c-Jun NH_2-terminal kinase (*JNK*), and Nuclear factor-κB (*NF-κB*), by preventing phosphorylation of p65 and the degradation of Inhibitor of κB (*IκB*), which in turn modulates macrophage chemotaxis at relatively low concentrations (100–200 μg/mL).[140,141] Thus, it could be applied in the treatment of chronic inflammation, such as rheumatoid arthritis and atherosclerosis, where macrophage infiltration into target tissues is a key pathological factor.

From a bioavailability and ADME perspective, ginger-derived phenolics are known to undergo rapid Phase II metabolism, resulting in low systemic exposure following oral administration. Fermentation may partially mitigate this limitation by increasing the relative abundance of more lipophilic metabolites, such as 6-shogaol, which may enhance intestinal permeability.[142–145] In addition, fermentation generated diverse secondary metabolites that may act synergistically potentially amplifying biological effects despite low concentrations of individual compounds.[95,146] Nevertheless, direct ADME investigations of fermented *Zingiberaceae* products remain scarce, and further studies are required to confirm whether fermentation meaningfully alters absorption, distribution, metabolism or excretion profiles in vivo.

In vivo investigations further indicate that fermented turmeric products may influence gut microbiota composition and metabolic health.[95,147–149] High-fat diet models consistently showed reduced microbial diversity, whereas dietary administration of fermented turmeric partially restored species richness and increased the relative abundance of *Akkermansia muciniphila*, a bacterium negatively associated with metabolic disorders. Proposed explanations include antioxidant-mediated support of anaerobic bacterial growth and increased mucin availability stimulated by bacterial components such as lipoteichoic acid.[150,151] Additionally, fermentation-derived oligosaccharides released from polysaccharide degradation may serve as substrates for microbial fermentation in the gut.[152–154] Although direct mechanistic pathways were not systematically investigated, the temporal association between altered phytochemicals composition and biological outcomes suggest that fermentation may enhance functional exposure to bioactive constituents in vivo.

These findings highlight the fermentation effects toward phytoconstituents and their pharmacological activities. Fermentation helps break down large plant molecules into much smaller particles with higher bioavailability, making

it easier to penetrate the dermal layers through the stratum corneum.[155–158] The results of this study show an increase in compounds (organic acids, amino acids, and polyphenols) after fermentation. The enhanced antioxidant activity, as tested by DPPH and FRAP assays, is attributed to the formation of new metabolites resulting from microbial bio decomposition, which stimulate the production of Collagen I and II, as well as protect elastin from enzymatic degradation in the Extracellular Matrix.[87,159–161] Furthermore, fermentation strengthens the epidermal barrier through the synthesis of key proteins, such as Loricrin and Filaggrin.[162–164] These proteins are critical in clinical practice for treating dry and sensitive skin, as their anti-inflammatory activity can suppress IL-8.[165–167] Additionally, toxicity testing revealed that FAA does not induce cytotoxicity in human skin cells, even at high concentrations, indicating it is safe for long-term use.[87] However, clinical validation remains necessary before therapeutic claims can be established.

Fermentation has emerged as a pivotal biotechnological strategy for modulating phytochemical profiles to enhance the pharmacological efficacy of medicinal plants. In the *Zingiberaceae* family, the primary transformation mechanisms focus on specific dehydration processes and the bioconversion of phenolic constituents. For instance, the fermentation of ginger (*Zingiber officinale*) by lactic acid bacteria triggers the conversion of 6-gingerol into 6-shogaol via the removal of water molecules.[58,133–135] This transformation is highly significant, as 6-shogaol exhibits superior chemical stability and more potent antioxidant and anti-inflammatory properties compared to its native form. This phenomenon is distinct when compared to the *Fabaceae* family (eg., soybean), where the dominant mechanism is not dehydration but rather enzymatic hydrolysis mediated by β-glucosidase. In *Fabaceae*, fermentation aims to cleave glycosidic bonds in isoflavone glycosides to release isoflavone aglycones (daidzein and genistein) from their sugar moieties.[68,75,168] Although both processes share the common goal of increasing lipophilicity and bioavailability, *Zingiberaceae* exhibits more complex internal structural alterations. These changes directly modulate pro-inflammatory cytokine signaling pathways, specifically the Mitogen-Activated Protein Kinase (*MAPK*) and Nuclear Factor-kappa B (*NF-kB*) pathways, at the cellular level.

Furthermore, when compared to the *Theaceae* family (as in the black tea production process), the mechanisms occurring in the *Zingiberaceae* family are reductive and selective, resulting in the production of small molecules.[169,170] In contrast, in *Theaceae*, fermentation via enzymatic oxidation often involves the polymerization of catechins into larger molecules such as teaflavins and tearubigins. Although these polymers provide unique sensory characteristics, these large molecules sometimes have limitations in penetrating biological layers. On the other hand, fermentation in the *Zingiberaceae* family produces much smaller particles that can penetrate the stratum corneum and dermal layers more effectively. This provides therapeutic advantages for the *Zingiberaceae* family in dermatological applications, such as the stimulation of type I and II collagen and the protection of elastin, which are not significantly observed in the fermentation products of the other plant families that produce large polyphenols.[87,171]

Differences in mechanisms are also clearly evident when comparing the *Zingiberaceae* family with the *Asteraceae* family. In the *Asteraceae*, fermentation is often focused on degrading the rigid lignocellulosic matrix of the cell wall to release bound phenolic.[172–174] Although this process increases the quantitative yield of active compounds, it also creates new secondary metabolites through microbial biological decomposition that possess a better safety (toxicity) profile.[175] Overall, other plant families use fermentation primarily to increase the concentration or solubility of compounds with low bioavailability into stable, lipophilic pharmacological agents with high affinity for biological targets in both in vitro and in vivo models.

Limitations of the Study

Although the present review provides comprehensive insights into the fermentation effects toward *Zingiberaceae* plants and phytoconstituents. This review has several limitations that should be acknowledged. Firstly, although enhance biological activity following fermentation was consistently reported, most studies relied on associative evidence, with limited direct validation of underlying molecular mechanism, such as enzyme-specific biotransformation pathways or metabolite-target interactions. Second, phytoconstituent characterization varied substantially across studies, with many relying on total phenolic or flavonoid content rather that comprehensive metabolic profiling, limiting direct comparability and synthesis. Furthermore, the absence of clinical validation and standardized outcomes measures limits translational interpretation. In addition, many in vitro and in vivo studies employed exposure levels that may not reflect achievable concentrations in humans, particularly given known ADME constraints of *Zingiberaceae*-derived compounds. These

limitations highlight the need for future studies integrating controlled fermentation parameters, targeted metabolomics, and translation models to strengthen causal inference and applicability.

Conclusion

This review elaborates an overview of the complex and multifaceted fermentation as biologically relevant and methodologically adaptable strategy to enhance the phytochemical profile and pharmacological potential of *Zingiberaceae* plants. These transformations are strongly influenced by fermentation parameters, particularly microbial strain selection, substrate composition, fermentation time, temperature, and oxygen availability, which together determine the direction of phytochemical changes. A key insight emerging from this review is the pronounced species specificity with *Zingiberaceae* family. Fermentation outcomes differ substantially among genera and species such as *Aframomum angustifolium, Amomum xanthioides, Curcuma longa* and *Zingiber officinale*. These specificities explain why similar fermentation approaches may enhance anti-inflammatory or antioxidant activity in one species while primarily improving antidiabetic effects in another. From a pharmacological perspective, converging in vitro and in vivo evidence demonstrates that fermentation frequently enhances biological activity compared to non-fermented extracts. Overall, fermentation represents a promising approach to unlock the therapeutic potential of *Zingiberaceae* phytoconstituents through controlled biotransformation. Future perspective should prioritize standardized fermentation protocols, comparative multi species studies, and mechanistic investigations linking specific microbial enzymes to pharmacological outcomes.

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Disclosure

The authors declared 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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