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The whole grain-bacteria tango: How fermentation enhances the release and health benefits of phenolic compounds

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ABSTRACT: Phenolic compounds in whole grains (WGs) are predominantly bound to dietary fibers, restricting their bioavailability and potential health benefits. Although growing studies are focusing on bacteria in fermented whole grains, how fermentation boosts phenolic compounds' release and health benefits is still not well understood. Here, we review the key microorganisms used in WG fermentation, along with the effects and potential mechanisms whereby microbial fermentation influences the release and transformation of phenolic compounds. Further, we summarize the latest progress in leveraging the health benefits of phenolic compounds in fermented WGs. Microbial fermentation significantly increases the content of free phenolic compounds by degrading cell wall matrices. Released phenolic compounds exhibit multifaceted health benefits. The application of omics technologies has further elucidated the microbial consortia and metabolic pathways involved. Understanding how microbial fermentation enhances the release of phenolic compounds in WGs is essential for their application in the food industry.

Keywords: fermentation; whole grains; phenolic compounds; health benefits; omics technologies

1. Introduction

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Whole grains (WGs) are recognized as exceptional foods with significant nutritional benefits for human health. Grains such as wheat, rice, maize, oats, barley, rye, millet, and sorghum are commonly consumed by humans^[1]. The fiber-rich bran, the nutrient-dense germ, and the starch-laden endosperm are the three key components in WGs^[2]. In contrast, refined grains are typically processed through grinding, crushing, and flaking, retaining only the endosperm and losing the germ and bran^[3]. Consequently, WGs offer a higher content of protein, minerals, vitamins, dietary fiber, and phytochemicals compared to their refined counterparts^[4] (Fig. 1). Numerous research studies, including those conducted by the World Health Organization, have shown that consuming more WGs is linked to significant health benefits^[4]. Recent evidence suggests that higher whole-grain consumption is correlated with lower risks of cardiovascular diseases, type 2 diabetes, cancer, and improved gut health^[5]. This is primarily due to its health-promoting components, such as dietary fiber and various bioactive compounds. The scientific consensus regarding the health advantages of whole grain foods has gained widespread recognition globally. Many countries, including China, the United Kingdom, the Netherlands, Denmark, Italy, and the United States, are vigorously promoting the development of the whole grain industry and advocating for the utilization of WGs and their products^[6]. Furthermore, the development and utilization of WGs can mitigate losses and waste within the food processing chain while enhancing grain yield. Therefore, researchers are increasingly interested in whole grains due to their potential to improve health and prevent diseases.

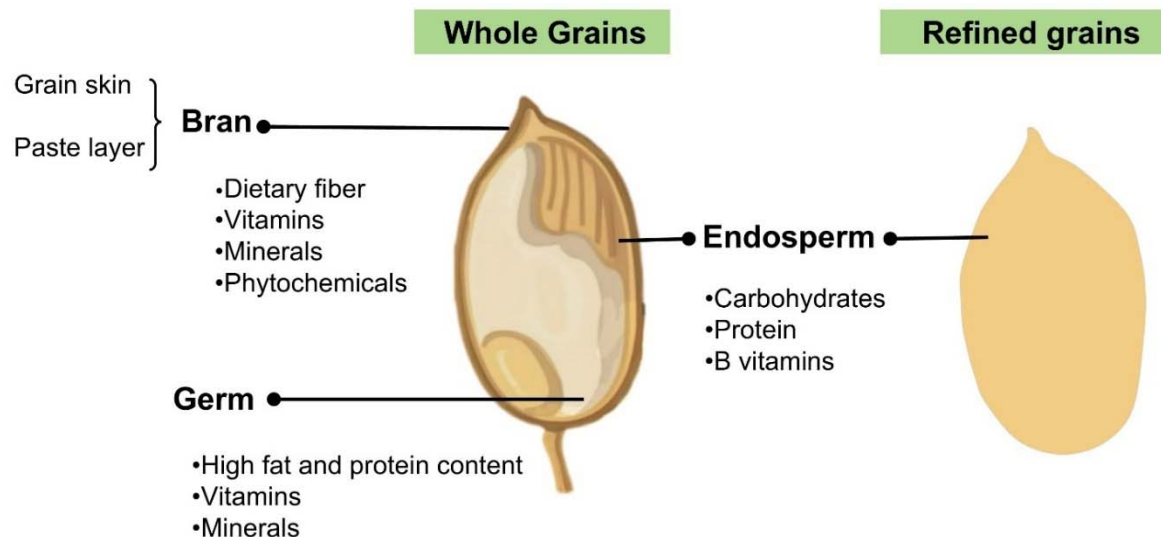


Fig. 1 The comparison of the structure and nutritional components between whole grains and refined grains.

In recent years, researchers have focused on the rich phenolic compounds, which primarily exist in the bran and germ layers in whole grains. Generally, these compounds can be classified into three categories based on their structural characteristics: flavonoids, phenolic acids, and tannins^[7]. These phenolic compounds, such as ferulic acid, caffeic acid, phytic acid, and various flavonoids, endow whole grains with significant antioxidant and anti-inflammatory properties, as well as the potential to prevent chronic diseases such as cardiovascular diseases and type 2 diabetes^[8, 9]. However, the phenolic compounds in WGs are primarily embedded in cell wall dietary fiber and covalently bound to structural polysaccharides, such as

arabinoxylan, via ester or ether bonds, which restricts their utilization in the natural state^[10]. Fermentation biotechnology has garnered renewed interest owing to its capacity to confer unique nutritional and functional attributes to food products. The fermentation process intentionally transforms or modifies substrates via the activities of microorganisms to achieve the desired effects. In particular, fermentation has been extensively utilized to enhance the bioavailability of phenolic compounds in whole grains by cleaving hydrogen and covalent bonds between phenolic compounds and other compounds^[11]. Several widely consumed whole grains, including oats, brown rice, and sorghum, have enhanced their phenolic content through fermentation^[12, 13]. Additionally, fermentation can enhance the properties and nutritional value of whole grains, making them more acceptable to consumers^[14].

However, the number of studies examining how fermentation affects the release of phenolic compounds is limited. The health benefits of these compounds are not well illustrated. Thus, this review aims to investigate how fermentation influences phenolic compounds in WGs by assessing the impact of essential microorganisms on their release and transformation. Moreover, we evaluate the potential health benefits of fermented WGs. By synthesizing current research, this review aims to establish a solid foundation and framework for future studies and practical applications of fermented whole-grain products.

2 Microorganism species in whole-grain fermentation

Traditionally, grain fermentation is initiated spontaneously by microorganisms present in the raw ingredients. This process can occur both at home and in small-scale industrial settings. A widely used technique is the backslopping method, which involves the introduction of previously fermented material as a starter culture^[15]. However, to enhance efficiency and ensure consistent product quality, controlled fermentation is gaining popularity. Recently, the controlled fermentation of whole grains using microorganisms such as lactic acid bacteria and yeast has become a trend. This discussion will primarily focus on the application of prevalent species in the fermentation of WGs (Table 1).

2.1 Lactic acid bacteria

Lactic acid bacteria (LAB) are a group of Gram-positive bacteria that can utilize fermentable carbohydrates to produce large amounts of lactic acid. During fermentation, LAB can produce organic acids and enzyme systems, such as proteases and carbohydrate enzymes. These metabolites enhance the antibacterial properties of LAB and improve food quality^[16]. They are the dominant microbial population in many traditional fermented grain foods, such as sourdough, fermented rice flour, and silage feed^[17-19]. *Lactobacillus*, *Leuconostoc*, *Pediococcus*, *Lactococcus*, and *Weissella* are commonly found among LAB in whole-grain fermentation environments. *Lactobacillus plantarum* is one of the most multifunctional and frequently isolated species, known for its strong adaptability to various substrates and broad enzyme spectrum. It excels in phytic acid degradation, peptide hydrolysis, and exopolysaccharide production^[20]. *Lactobacillus brevis* is often associated with the fermentation of grains and sourdough, contributing to the production of acetic acid and heterofermentative metabolism. *Lactobacillus sanfranciscensis* is a key symbiotic bacterium in traditional sourdough, renowned for its efficient maltose metabolism and the

production of antibacterial compounds [21]. Other notable species include *Lactobacillus fermentum*, *Lactobacillus casei*, and *Lactobacillus rhamnosus*, which are often valued for their probiotic potential[21].

LAB secretes various enzymes that target the complex matrix of whole grains. Phytase is crucial for hydrolyzing phytic acid, thereby releasing bound minerals such as iron, zinc, and calcium, and significantly enhancing their bioavailability[22]. Amylase and xylanase break down starch and arabinoxylan, respectively, modulating blood glucose responses and generating prebiotic oligosaccharides. Protease hydrolyzes storage proteins into peptides and free amino acids, which not only improves protein digestibility but also releases bioactive peptides with antioxidant, anti-inflammatory, and ACE-inhibitory activities. Notably, LAB can also secrete various hydrolytic enzymes such as xylanase, cellulase, and feruloyl esterase, effectively deconstructing the heterogeneous polysaccharide network of cereal cell walls, thereby releasing phenolic compounds. In addition to the release of combined phenolic substances, microbial fermentation also participates in the conversion of phenolic compounds into new metabolites, such as ferulic acid and caffeic acid derivatives[23].

2.2 Yeasts

Yeasts are a group of unicellular eukaryotic microorganisms classified within the Fungi kingdom and widely distributed throughout the natural environment. In the fermentation of WGs, *Saccharomyces cerevisiae* is the most utilized strain. Yeast uses fermentable sugars (glucose, maltose, sucrose) in grains for aerobic respiration or anaerobic fermentation[24]. Under anaerobic conditions, yeast converts glucose into ethanol and carbon dioxide through a process known as glycolysis. The carbon dioxide produced is what makes bread, steamed buns, and other fermented flour products fluffy[25]. The various by-products generated, including higher alcohols, esters, organic acids, aldehydes, and ketones, significantly contribute to the product's unique flavor profile[26].

Yeast primarily plays a role in the fermentation process by breaking down substrates and producing metabolic products. Yu et al. utilized yeast for the solid-state fermentation of sweet sorghum to produce ethanol, where the amylase and cellulase produced by yeast can decompose starch and cellulose in sweet sorghum, thereby enhancing ethanol yield[27]. Similarly, Ilowefah et al. employed yeast for the solid-state fermentation of brown rice flour, during which the proteases secreted by yeast hydrolyze the proteins in brown rice flour, promoting the proliferation or accumulation of amino acids and peptides within the yeast cells[28]. The cellulases, xylanases, and amylases secreted by yeast can hydrolyze phenolic compounds in the cell wall matrix, facilitating the release of these phenolic substances, resulting in an increase in total phenolic content after fermentation[29]. Furthermore, other hydrolytic enzymes secreted by yeast, such as β -glucosidase from *Saccharomyces cerevisiae*, can promote the separation of phenolic compounds from glycosides, thereby releasing free phenolic acids and enhancing their biological activity[30]. Certain strains of yeast can secrete phytase, which hydrolyzes phytate in whole grains, improving the nutritional quality of whole grains[31].

Filamentous fungi are the most widely used microorganisms in solid-state fermentation. These fungi naturally grow by infiltrating the substrate particles with their mycelium and secreting hydrolytic enzymes that break down the insoluble components of the substrate's cell wall, resulting in small molecular nutrients that accelerate the growth of the strains and the transformation of nutrients. *Aspergillus* and *Rhizopus* are the most commonly used fungi in the fermentation of grains and legumes, effectively increasing the content of bioactive substances and antioxidant capacity. They are widely applied in the recycling of agricultural food waste and by-products, and can enhance their added value by obtaining enzymes and various bioactive substances. The glycosidases, xylanases, amylases, and proteases produced during fungal fermentation can promote the degradation of bioactive components such as polyphenols, polysaccharides, and polypeptides. Many fungi have great potential in fermenting WGs. These include *Aspergillus oryzae*^[32], *Aspergillus niger*^[33], *Aspergillus awamori*^[34], etc. Edible fungi exhibit significant potential in the fermentation process. A study employed Brazilian oyster mushrooms and double-spored oyster mushrooms to perform solid-state fermentation on whole wheat. The fermentation processes notably altered the polyphenol content and the composition of phenolic compounds in wheat^[35].

2.3 Other newly isolated strains and uncultivated microbial communities

Recently, due to the intricate structure of whole grain substrates, which are abundant in dietary fiber and contain significant amounts of bound phenolic compounds, researchers have increasingly focused on screening new strains with specific functions while also exploring the potential roles of uncultured microbial communities. Given the structure of WGs and their fermentation environment, newly isolated strains should exhibit enzymatic activity that efficiently decomposes complex carbohydrates, such as starch and cellulose, as well as anti-nutritional factors like phytic acid. Moreover, these strains must be able to tolerate the fermentation environment and produce beneficial metabolic products. Researchers isolated a hemicellulolytic and cellulase-producing fungus, *E. parvum* 4-14, from soil, which produces highly active, heat-resistant enzymes, including CMCase, β -glucosidase, xylanase, and FAE during solid-state fermentation^[36]. Their findings indicated that this enzymatic system shows significant effectiveness in liberating ferulic acid from wheat bran. Researchers have also isolated various strains with probiotic properties from natural foods and fermented products, which can be utilized in the fermentation of WGs^[37]. New strains that better meet requirements can be cultivated using specific culture media. Research was conducted on the use of yeast culture YB1 (*Meyerozyma guilliermondii*) in the production of type II yeast from ordinary wheat flour. The results demonstrate that the new yeast has a significant advantage in improving the characteristics of fermentation products^[38].

3 Mechanism of the release and transformation of phenolic compounds during whole-grain fermentation

Phenolic compounds found in WGs primarily occur in both free and bound states, and their distribution as well as their content can vary considerably depending on the grain type and the tissue involved. Free phenolic compounds can be readily dissolved in water or organic solvents, whereas bound phenolic

compounds are associated with cell wall polysaccharides, proteins, or lignin through ester, ether, or glycosidic bonds, and are primarily located in the bran and germ of grains^[39]. The proportion of bound phenolics within the total phenolic content varies among cereal species; for example, bound phenolic acids constitute 50-60% of the total phenols in barley and rye, whereas this proportion can rise to 80% in maize^[40]. In contrast to most phenolic compounds, which have low bioavailability due to their structural properties, oats contain a rich supply of oat alkaloids, a unique type of phenolic compound recognized for its strong anti-inflammatory and antioxidant effects^[41]. This variation in distribution is linked to plant defense mechanisms, where bound phenolics enhance cell wall structure to protect against pathogen invasion. It has been proven that bound phenolic compounds have significant health benefits. However, and only 25% of bound phenolic compounds can be released through fermentation by colonic microorganisms. As illustrated in Fig. 2, fermentation degrades these structures through enzymatic action and the synergistic activity of microorganisms, resulting in the release of phenolic compounds.

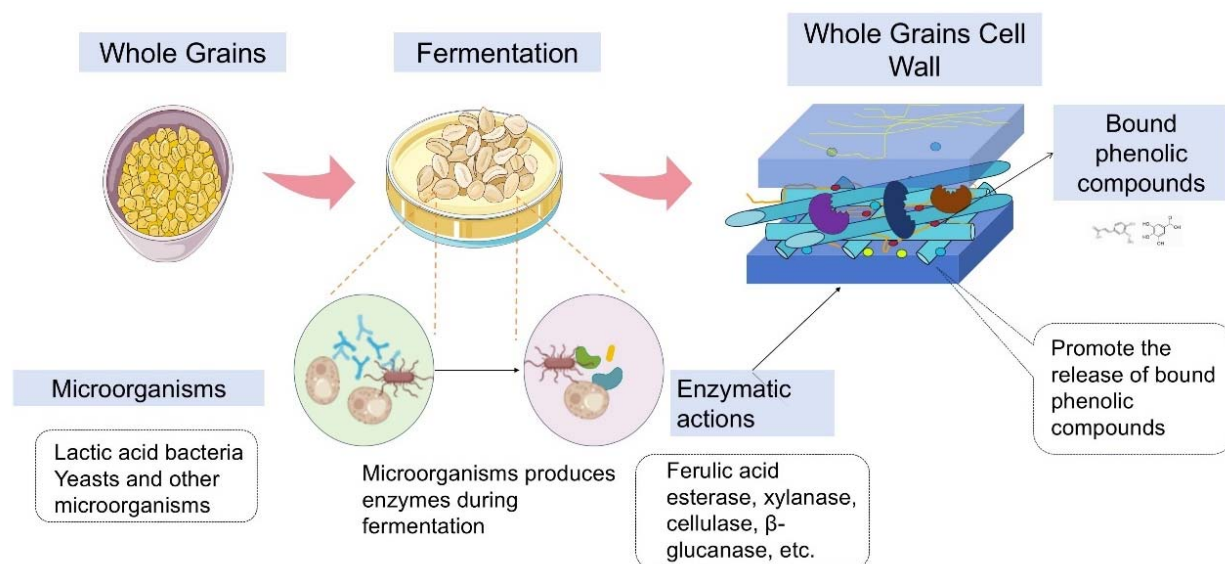


Fig. 2 The microorganisms and enzymes during fermentation and their mechanism of action in promoting the release of free phenolic compounds.

3.1 Enzymatic actions

Many food processing technologies have been employed to liberate bound phenolic compounds from WGs and their by-products, including chemical hydrolysis and physical treatments^[42]. However, these methods often only moderately enhance the concentration of free phenolic compounds or are unsuitable for food material processing due to safety concerns. In contrast, enzymatic hydrolysis has emerged as a promising method for effectively releasing bound phenolic compounds, owing to its mild reaction conditions and environmental advantages.

Based on the types of covalent bonds between phenolic compounds and cell wall polysaccharides (primarily ester and glycosidic bonds), the enzymes responsible for releasing these compounds can be divided into two major categories. The first category consists of ester hydrolases, represented by ferulic esterase, which specifically hydrolyzes the ester bond between ferulic acid and arabinose in hemicellulose,

releasing free ferulic acid and other phenolic acids^[43]. The second category consists of glycosidase enzymes. Among these, β -glucosidase hydrolyzes the glycosidic bonds of phenolic glycosides (such as bound protogallic acid) to produce the aglycone^[44]. Cellulases (including endoglucanases and exoglucanases) and xylanases, on the other hand, break down the cellulose and hemicellulose frameworks, thereby releasing polyphenols that are physically bound or covalently linked^[45]. Numerous studies have confirmed the role of these enzymes. In fermentation experiments with oats (*Avena sativa* L.), cellulases effectively released and converted phenolic compounds by breaking down cell wall structures, significantly increasing their content and bioavailability^[46]. In an experiment involving the fermentation of barley by *Lactobacillus plantarum* dy-1, the 6-phosphoglucuronidase produced by the strain hydrolyzed the glycosidic bond between the phenolic group and the sugar moiety, converting bound phenols into free phenols^[47]. A novel ferulic acid esterase isolated from *Burkholderia pyrrocinia* strain B1213 efficiently hydrolyzes the ester bonds of substrates such as methyl ferulate in wheat bran, releasing ferulic acid^[48].

Germination technology can also effectively release bound phenolic compounds by activating the endogenous enzyme system of whole grain seeds. During germination, the seeds absorb water and swell, endogenous enzyme activity increases, triggering a series of ordered physiological reactions that lead to changes in cell wall structure^[49]. In recent years, this technology has been applied to various WGs, including buckwheat, brown rice, oats, and quinoa^[49, 50]. Typically, within 72 hours of germination, the content of total phenols and other bioactive compounds increases significantly over time, primarily due to the degradation of cell walls by endogenous enzymes^[49].

3.2 Enhanced release of phenolic compounds by microorganisms

Microorganisms release bound phenolic compounds by secreting enzymes. The differences in the enzyme systems secreted by different microorganisms determine their ability to hydrolyze grain cell walls. The effect of different microorganism fermentation on the enhancement of phenolic compounds release in WGs by secreting enzymes were summarized in Table 1. Bacteria (especially LAB) have the advantage of secreting phenolic ester hydrolases such as ferulic esterase and coumaric esterase, as well as acidifying the environment through acid production to loosen cell wall structures. Their metabolic pathways can also convert phenolic acids into more active derivatives^[51]. Fungi (such as yeast, *Monascus purpureus*, and *Aspergillus oryzae*) are adept at secreting cell wall-degrading enzymes and proteases, which can efficiently break down the physical barriers of grain bran.

Table 1 Studies on the effect of microbial fermentation on phenolic compounds in WGs.

Microorganisms		Whole grains/substrate	Enzyme	Main findings	References
Lactic acid bacteria	<i>Lactiplantibacillus plantarum</i> dy-1	Barley bran	Sulfatase	Ester bonds between bound phenolic acids and cell wall polysaccharides in hydrolyzed barley bran dietary fiber.	[124]
	<i>Bacillus subtilis</i>	<i>Zea mays</i> L.	Cellulase, β -glucosidase, and xylanase	It disrupted the cellular structure of the corn and weakened the interactions between the bound phenolic compounds and the food matrix.	[125]
	<i>L. plantarum</i> Dy-1	Barley	β -glucosidase	Secretes 6-phosphate- β -glucosidase (LPBG); hydrolyzes phenolic glycosidic bonds, converting bound phenols to free phenols.	[47]
	<i>Lactobacillus fermentum</i>	Wheat bran	Feruloyl esterases	Increases the release of ferulic acid; when used in combination with xylanase, the effect is even more pronounced.	[126]
Yeast	<i>Saccharomyces cerevisiae</i>	Wheat bran and oat bran	-	Significantly increase the phenolic acid contents.	[127]
	<i>Saccharomyces cerevisiae</i>	Wheat bran	-	Total phenol content increased. Combined with increased polyphenol and flavonoid content.	[128]
	<i>Monascus purpureus</i>	Sorghum bicolor	-	After fermentation, the levels of various phenolic compounds increased many-fold.	[129]
Fungi	<i>Aspergillus niger</i> , <i>Aspergillus oryzae</i> and <i>Aspergillus awamori</i>	Wheat bran	Cell wall-degrading enzymes, such as β -glucosidase, cellulase, and xylanase.	Break down cell wall structures and promote the release of phenolic compounds.	[130]
	<i>Aspergillus oryzae</i>	Whole intermediate wheatgrass	-	Total phenolic content and total flavonoid content peaked on days 4–5, followed by a slight decline in the days that followed.	[131]
Blended/Co-fermentation	<i>Monascus anka</i> , <i>Saccharomyces cerevisiae</i> and <i>Bacillus subtilis</i>	Corn seeds (<i>Zea mays</i> L.)	Cellulase activity has increased.	Enzymes produced by microorganisms break down the cellular structure of corn, causing the bonds to be hydrolyzed, which in turn leads to the release of phenolic compounds.	[43]
	<i>L. acidophilus</i> , <i>reuteri</i> , and	<i>L.</i> Whole-grain highland barley	-	Solid-state fermentation significantly increased the	[132]

<i>Enterococcus faecalis</i>		soluble dietary fiber and total polyphenol content and altered the structural integrity of whole-grain and flour from highland barley.	
<i>Lactiplantibacillus plantarum</i> , <i>Saccharomyces cerevisiae</i> , <i>Rhizopus oryzae</i> , <i>Aspergillus oryzae</i> , and <i>Neurospora sitophila</i>	Sorghum grain	The activities of polyphenol oxidase, β -glucosidase, and cellulase increased, respectively.	Cellulase promotes the degradation of tannins and phenolic compounds; xylanase releases flavonoids. [133]

Beyond the enzyme activities of individual species, mixed-culture fermentation often achieves superior phenolic release through two synergistic mechanisms: cross-feeding and enzymatic complementarity. Cross-feeding refers to a process in which metabolic products secreted by one microorganism are utilized by another as essential nutrients, thereby promoting the growth and metabolic activity of both partners. For instance, in the co-culture of *Saccharomyces cerevisiae* and *Lactobacillus plantarum*, yeast secretes a pool of amino acids, which enables the survival and proliferation of LAB that have specific amino acid auxotrophies. Conversely, LAB degrade lactose into simple sugars such as glucose and galactose, providing a carbon source for yeast, thereby forming a bidirectional cross-feeding relationship^[52]. This mechanism has also been observed in other systems; for example, the *Sporolactobacillus* sp. LBM15018 performs unidirectional cross-feeding with *Caproicibacterium lactatifermentans*, delivering lactate as a substrate for caproate production, thereby overcoming carbon source utilization limitations that hinder single-strain fermentation^[53].

Cross-feeding does not operate in isolation; it often converges with enzymatic complementarity to create a self-amplifying loop for phenolic release. Enzymatic complementarity occurs when enzymes secreted by different microorganisms target distinct substrates or different sites of the same macromolecule, collectively achieving a degradation outcome that exceeds the sum of individual activities. Recent studies have shown that microorganisms can form synergistic metabolic networks through the integration of cross-feeding and enzymatic complementarity. Taking whole wheat dough co-fermentation as an example, Li et al. found that when *L. plantarum* and *S. cerevisiae* were co-cultured, the organic acids produced by LAB activated endogenous grain xylanases, which hydrolyzed the arabinoxylan backbone to expose ferulic acid binding sites^[54]. Concurrently, LAB secreted ferulic acid esterase (FAE) that cleaved the ester bonds to release free ferulic acid. This enzyme-complementary mechanism increased ferulic acid release by 2.4-fold compared to yeast fermentation alone^[54].

The practical benefits of these synergistic interactions have been validated across multiple grain fermentation systems. Researchers conducted co-fermentation of brown rice using *L. plantarum* and *S. cerevisiae*, and the results showed that free ferulic acid content increased 2.8-fold and hydroxybenzoic acid content increased 3.1-fold compared to raw rice, outperforming single-strain treatments^[45]. Similarly, mixed cultures of *Monascus purpureus* and *Bacillus subtilis* increased total phenolic acid content in corn (*Zea mays*

L.) by 40–60% through the production of synergistic enzymes^[43], while also reducing antinutritional factors such as phytic acid by 70–90% and thereby releasing phenolic compounds that were previously chelated to minerals^[52]. More recently, mixed fermentation of *L. plantarum* and *S. cerevisiae* in pigmented quinoa significantly increased free phenol content to 3.15–4.36 mg GAE/g DW, with fermented black quinoa exhibiting 109% and 297% enhancements in DPPH radical scavenging capacity and total reducing capacity, respectively^[53]. These findings collectively demonstrate that the "tango" interaction between different microbial species is not a simple additive effect but a programmed interplay of enzymatic complementarity and cross-feeding, each reinforcing the other. The metabolic network mechanism was shown in Fig. 3.

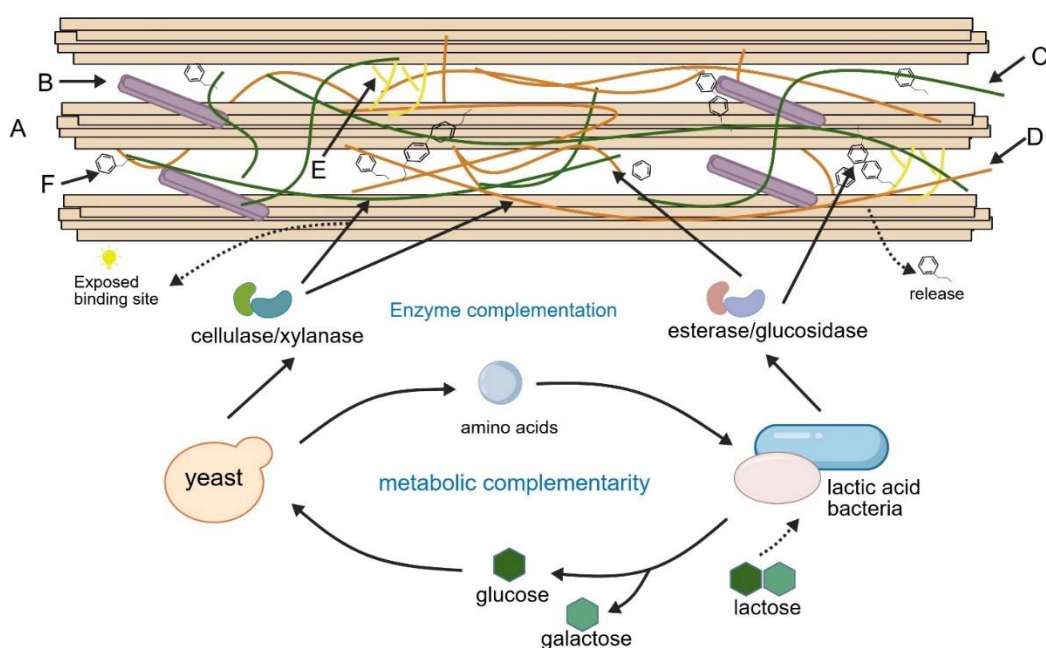


Fig. 3 Synergistic metabolic networks among different microorganisms. **Microorganisms influence each other's growth and metabolism through product complementarity; they also work together to promote the release of phenolic compounds by producing different types of enzymes.**

In addition to secreting hydrolytic enzymes, the metabolic activities of microorganisms themselves can directly convert phenolic compounds. Plant-derived lactobacilli can convert phenolic acids (such as cinnamic acid) accumulated during germination into more bioactive derivatives (such as gentisic acid, protocatechuic acid, and 4-hydroxyphenethyl alcohol) through the phenylalanine/tyrosine metabolic pathway^[51]. There are significant differences among microbial strains in terms of their metabolic capabilities and pathways for phenolic compounds. In wheat and rye sourdough, *Lactobacillus plantarum* is capable of metabolizing free ferulic acid, while *Lactobacillus hammesii* can metabolize vanillic acid and eugenol, thereby reducing the content of bound ferulic acid^[55]. The genomes of certain strains may encode genes responsible for phenolic compound metabolism, while other strains may lack these capabilities. The type and composition of fermentation substrates influence the expression and activity of microbial enzymes, thereby determining the metabolic pathways of phenolic compounds^[56]. Furthermore, microbial transformation of phenolic compounds may enhance, reduce, or maintain their antimicrobial activity.

3.3 Optimizing fermentation parameters to influence phenolic bioaccessibility

As noted, two main mechanisms enhance the bioaccessibility of phenolic compounds: direct enzymatic action and microbial promotion of phenolic release. Both depend heavily on fermentation parameters. Phenolic bioaccessibility sets the upper limit of health benefits from fermented WGs, so optimizing fermentation parameters is more practical than simply increasing phenolic yields. Fermentation parameters work through two pathways: directly regulating key enzyme activities and indirectly affecting microbial growth, metabolism, and enzyme profiles.

Specifically, temperature directly determines enzyme catalytic rate and thermostability, while also regulating microbial proliferation. Adebo et al. found in their study on the fermentation of whole-grain sorghum that optimal temperatures can significantly increase total phenolic and flavonoid content, as well as antioxidant activity, by regulating microbial growth and metabolic activity^[57]. pH influences the formation of dominant microbial communities; LAB are acid-tolerant, whereas certain fungi are inhibited at low pH^[58]. Moisture content affects enzyme diffusion and substrate accessibility, while also determining microbial community structure. Yao et al. reported that moisture content was positively correlated with microbial α -diversity in solid-state Daqu fermentation, with decreasing moisture driving microbial succession and functional enzyme expression^[59]. Fermentation duration must align with both the microbial growth cycle and the temporal changes in enzyme activity. Tong et al. found that the microbial community during early fermentation (days 0–8) exhibited the greatest potential for caffeic acid synthesis, indicating that fermentation duration influences the expression of enzymes involved in phenolic acid metabolism^[60]. Research on the above mechanisms provides valuable insights for the controlled fermentation of WGs and their transition to industrial-scale production.

3.4 Crosstalk between food matrix and the gut microbiota *in vitro* fecal fermentation

As mentioned earlier, microorganisms play a key role in the fermentation of WGs, but they typically originate from fermentation starters or the natural environment. With the growing advocacy for whole grain consumption, it is crucial to understand the role of WGs and their bioactive components in the human gut. In the colon, undigested components (eg. bound phenolic compounds and fermentable fiber) interact with the gut microbiota. *In vitro* fecal fermentation models simulate the colonic environment under controlled conditions and are used to analyze how food matrices influence microbial composition and activity, as well as how microbes transform substrates and metabolize phenolic compounds (Fig. 4).

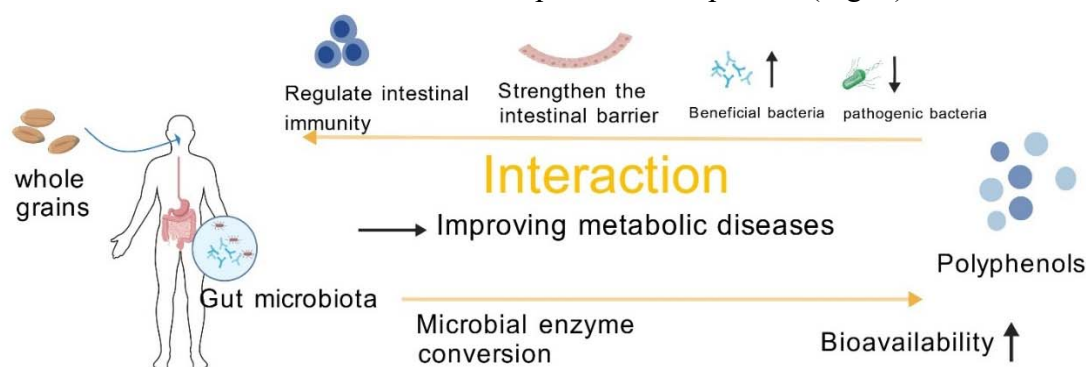


Fig. 4 The reciprocal relationship between fermented whole-grain polyphenols and gut microbiota.

Note: SCFAs, short-chain fatty acids.

The complexity of the structure of whole-grain matrices determines their interaction patterns with the colonic microbiota. The insoluble fibers in bran (such as cellulose and hemicellulose) serve not only as fermentable nutrients but also provide attachment sites for bacteria^[61]. Soluble fibers, including β -glucan and arabinoxylan, along with resistant starch, serve as primary carbon sources for glycolytic bacteria^[62]. In vitro fermentation experiments clearly demonstrate that bacterial populations such as *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, and *Enterococcus* preferentially utilize these soluble components, thereby becoming selectively enriched.^[63] The fermentation of these carbohydrates produces large amounts of short-chain fatty acids (SCFAs), primarily acetic, propionic, and butyric acids, and leads to a decrease in intestinal pH^[64]. SCFAs can regulate metabolism, improve immune function, and maintain the stability of the intestinal barrier^[65].

Most phenolic compounds in WGs exist in a bound form and have low bioavailability. Phenolic compounds not absorbed by the small intestine (approximately 90%–95%) enter the colon, where they undergo reactions such as deglycosylation, dihydroxylation, and decarboxylation under the action of gut microbiota and the enzymes they secrete (e.g., esterases and glycosidases), resulting in their release or conversion into smaller, bioactive metabolites^[66, 67]. For example, *Lactobacillus* species use esterases to convert ferulic acid into 4-vinylguaiacol and hydroxyferulic acid, ultimately generating vanillic acid and caffeic acid, which possess anti-Alzheimer's disease activity^[68]. Germinal animal studies have shown that in the absence of gut microbiota, the production of phenolic ring-opening degradation products (such as phenylpropionic acid and phenylacetic acid) is reduced by 70%–80%^[69], highlighting the indispensability of the microbiota.

Fermentation products (SCFAs and phenolic metabolites) are not produced in a one-way process; rather, they regulate the microbial community itself, creating a synergistic environment conducive to health. In vitro fermentation experiments have confirmed that phenolic extracts from WGs can significantly influence the composition of the gut microbiota. For example, following simulated colonic fermentation, phenolic metabolites such as protocatechuic acid, chlorogenic acid, caffeic acid, and p-coumaric acid were detected, accompanied by a decrease in the ratio of Bacteroidetes to Firmicutes and a reduction in the abundance of Proteobacteria^[70]. Phenolic acids from whole wheat can improve dysbiosis in a type 2 diabetes model, promoting the growth of beneficial bacteria and inhibiting harmful bacteria^[71]. Similarly, phenolic compounds bound to rice bran can inhibit the proliferation of harmful bacteria in human fecal cultures^[72]. Oat phenolic compounds have been shown to regulate glucose and lipid metabolism^[73]. Furthermore, in vitro studies have demonstrated that anthocyanins, chlorogenic acid, caffeic acid, cinnamic acid, and protogallic acid can all influence the composition of the human fecal microbiota^[74]. In summary, in vitro fecal fermentation models provide a robust platform for elucidating the “substrate-metabolite-feedback” dynamic relationship between whole grain substrates and the gut microbiota, and offer a scientific basis for the development of dietary intervention strategies.

4 Health benefits of phenolic compounds in fermented whole-grains

The prevalence of high-fat and high-sugar diets has contributed to a global increase in lipid and glucose metabolism disorders and related chronic diseases, such as obesity, type 2 diabetes (T2DM), and cardiovascular diseases, posing significant public health challenges. Although conventional pharmacological treatments are effective, long-term use is often accompanied by adverse effects, motivating researchers to explore safer bioactive compounds from natural sources. Phenolic compounds, especially polyphenols, are widely distributed plant secondary metabolites with well-documented bioactivities. Fermented WGs are particularly rich in phenolics, which are highly bioavailable and can exert multiple health-promoting effects, including the regulation of lipid and glucose metabolism, enhancement of gut barrier function, neuroprotection, and immune modulation (Fig. 5).

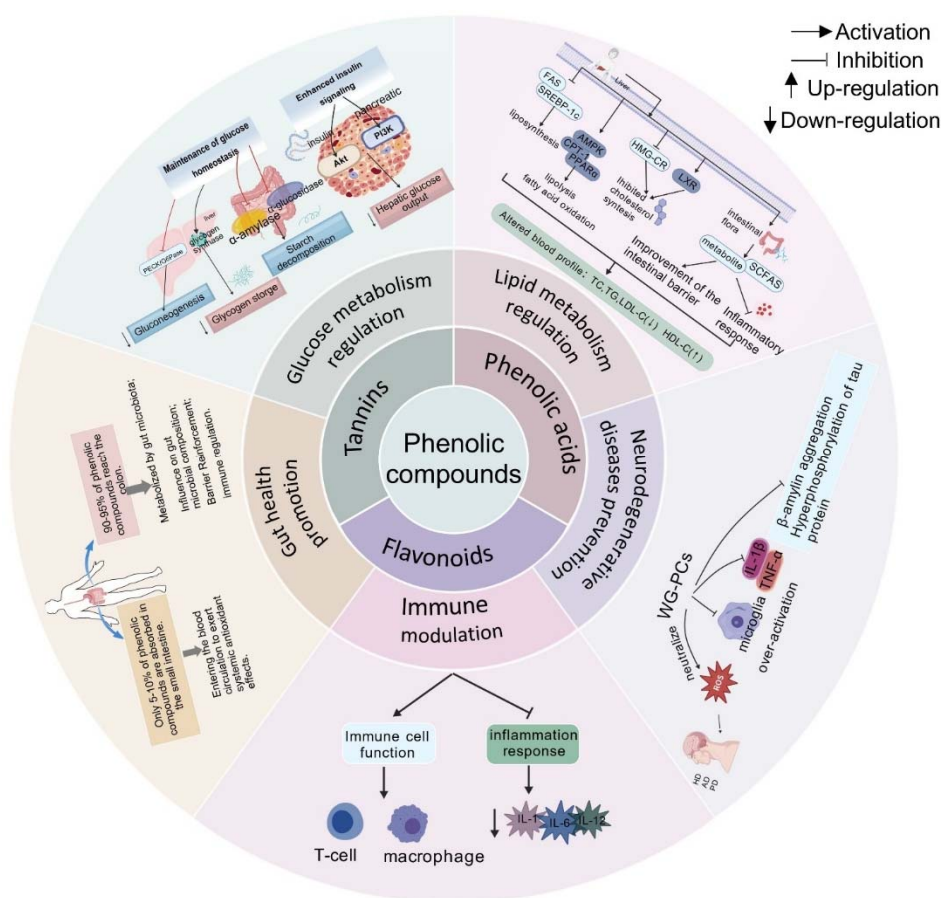


Fig. 5 The health benefits of phenolic compounds in fermented whole grains. Phenolic compounds regulate lipid metabolism by controlling fat and cholesterol synthesis and reducing oxidative stress through gut microbiota metabolites.

Phenolic compounds maintain blood sugar levels by enhancing insulin sensitivity and pancreatic function. Phenolic compounds undergo two metabolic pathways in the intestine. A small portion is directly absorbed by the small intestine and exerts antioxidant effects, while the majority regulates the ratio of intestinal flora to maintain intestinal barrier function. Phenolic compounds exert neuroprotective effects by neutralizing reactive oxygen species, inhibiting excessive activation of microglia and pro-inflammatory cytokines, interfering with the aggregation process of β -amyloid, and inhibiting excessive phosphorylation of tau protein. They also regulate the immune system by modulating immune cells and suppressing inflammatory responses.

Note: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; FFA, free fatty acids; FAS, fatty acid synthase; SREBP-1c, statins-regulated element-binding protein; AMPK, AMP-activated protein kinase; CPT-1, carnitine palmitoyltransferase-1; PPAR α , peroxisome proliferator-activated receptor alpha; HMG-CoA, a key intermediate in the cholesterol synthesis pathway; LXR, liver X receptor; IL-1, IL-6, IL-12, cytokines; PI3K/AKT, an intracellular signaling cascade, plays a key role in regulating the cell cycle, proliferation, and survival; PEPCK, key gluconeogenic enzymes; IL-1 β and TNF- α , pro-inflammatory cytokines.

4.1 Modulation of lipid metabolism

High-fat diets disrupt lipid homeostasis, characterized by elevated total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), along with decreased high-density lipoprotein cholesterol (HDL-C) levels^[75, 76]. Dyslipidemia is a major risk factor for obesity, hyperlipidemia, T2DM, and hypertension. While statins are widely prescribed and effective in reducing blood lipids, long-term use may cause gastrointestinal disturbances, myopathy, and hepatotoxicity^[77, 78].

Preclinical studies demonstrate that polyphenols can regulate lipid metabolism via multiple mechanisms. They suppress the expression of fatty acid synthase (FAS) and sterol regulatory element-binding protein 1c (SREBP-1c), activate AMP-activated protein kinase (AMPK) signaling and peroxisome proliferator-activated receptor α (PPAR α), thereby promoting lipolysis and fatty acid oxidation. Notably, the effects of specific phenolic compounds on lipid metabolism exhibit a dose-dependent relationship; for instance, moderate to high doses of anthocyanins or flavanols have been shown to produce greater reductions in TC and LDL-C compared to low doses, whereas excessive doses may not confer additional benefits and could even lead to pro-oxidant effects in certain contexts^[79]. Moreover, polyphenols inhibit HMG-CoA (a cholesterol precursor) reductase and activate liver X receptor (LXR), enhancing LDL-C clearance^[80]. In high-fat diet-induced C57BL/6J mice, supplementation with rice bran phenolic extracts significantly improved serum lipid profiles, reducing TC, TG, and LDL-C while increasing HDL-C^[81].

Clinical evidence remains limited. Polyphenols are generally recognized as safe with few adverse events at dietary intake levels, offering a favorable safety profile relative to long-term statin therapy; however, high-dose purified supplements require caution due to potential gastrointestinal discomfort or interactions with other drugs^[82]. A meta-analysis that included 46 RCTs involving 2,494 participants showed that polyphenols significantly reduced both systolic and diastolic blood pressure, while purified polyphenol extracts were also effective in lowering total cholesterol and triglycerides^[83]. Another study involving 54 patients with metabolic syndrome found that, following a 12-week whole-grain diet, increased concentrations of lipid and polyphenol metabolites were associated with a significant reduction in postprandial insulin and triglyceride responses^[84].

4.2 Regulation of glucose metabolism

T2DM affects approximately 10.5% of the global population, with impaired glucose metabolism being a hallmark feature^[85, 86]. Polyphenols have been demonstrated potential in improving glycemic control and insulin sensitivity in animal and in vitro studies. Whole-grain sorghum is rich in flavonoids and condensed tannins, which reduce fasting glucose levels and homeostatic model assessment for insulin resistance (HOMA-IR) while enhancing pancreatic function. Polyphenols from rye inhibit α -amylase and α -glucosidase activities, exhibiting antihyperglycemic effects^[87]. Ferulic acid, a representative hydroxycinnamic acid in WGs, suppresses the expression of gluconeogenic enzymes PEPCK and G6Pase and activates the IRS/PI3K/Akt/FoxO1 pathway, reducing hepatic glucose output^[88, 89]. It is worth noting

that the hypoglycemic effects of specific phenolic compounds exhibit a dose-dependent relationship, a finding that has been confirmed in healthy adults. In patients with type 2 diabetes, resveratrol demonstrated significant dose-response effects on blood glucose, glycated hemoglobin, and insulin levels^[90]. WGs rich in polyphenols can significantly reduce the need for insulin secretion and improve blood glucose fluctuations. In a single-blind RCT involving individuals with prediabetes, Almaski et al. compared the postprandial metabolic responses of millet muffins rich in polyphenols and dietary fiber with those of regular wheat muffins^[91]. The results showed that the millet muffins significantly reduced the 3-hour postprandial insulin increment in individuals with prediabetes and were associated with lower blood glucose peaks. Moreover, the efficacy of polyphenol intervention may depend on the disease severity of enrolled subgroups: a systematic review and meta-analysis found that polyphenol supplementation significantly reduced HbA1c specifically in patients with established T2DM (mean baseline HbA1c = 7.44%, reduction -0.21 ± 0.04 units), whereas no significant effect was observed in non-diabetic or pre-diabetic subjects^[92].

4.3 Promotion of gut health

The majority of dietary polyphenols (approximately 90–95%) are not absorbed in the small intestine and reach the colon, where they are metabolized by gut microbiota into low-molecular-weight compounds with higher bioavailability^[93]. Preclinical studies demonstrate that polyphenols act as prebiotics, selectively promoting beneficial bacterial growth, enhancing the production of SCFAs, and improving gut barrier function, which collectively mitigate systemic inflammation^[94, 95]. Polyphenol-rich WGs have been shown to modulate gut microbiota. Animal studies have provided compelling evidence for the gut-protective effects of whole grain polyphenols. In a murine model of dextran sulfate sodium (DSS)-induced colitis, supplementation with oat polyphenol extracts significantly attenuated inflammation, preserved mucosal architecture, and restored microbial diversity, including increased abundance of beneficial genera such as *Lactobacillus* and *Bifidobacterium*^[96]. Human intervention studies have also provided strong evidence. An RCT involving 67 overweight/obese participants found that a daily supplement of 27 g of wheat bran for 4 weeks significantly increased the abundance of *Bifidobacterium* and *Lactobacillus* in feces^[97]. Urinary metabolomics revealed a significant increase in polyphenol metabolites (including cinnamic acid, benzoic acid, and ferulic acid), demonstrating that whole-grain polyphenols can be metabolized by the gut microbiota and modulate its composition.

Gut microbes can metabolize bound phenolics (e.g., ferulic acid esters) into SCFAs such as butyric acid and propionic acid. These metabolites provided energy to colonocytes and reduced systemic inflammation by inhibiting pro-inflammatory factors, including TNF- α and IL-6^[94]. The 3-deoxyanthocyanidins present in sorghum, when combined with starch, have been shown to reduce postprandial blood glucose spikes by 28% and exert an anti-inflammatory effect by decreasing intestinal IL-8 secretion by 45% through the inhibition of the NF- κ B pathway^[95].

4.4 Prevention of neurodegenerative diseases

Neurodegenerative diseases (NDs), including Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by progressive neuronal loss and cognitive decline^[98]. Accumulating evidence suggested that oxidative stress, neuroinflammation, and protein misfolding play pivotal roles in the pathogenesis of NDs^[99]. Dietary interventions, particularly those rich in bioactive compounds, have garnered attention for their potential neuroprotective effects.

Polyphenols may prevent neurodegenerative diseases through various mechanisms. First, its powerful antioxidant capacity can effectively neutralize excess reactive oxygen species in the brain, reducing oxidative stress damage to neurons. Animal studies have shown that when exposed to oxidative stress induced by a high-fat diet, millet polyphenols exert a neuroprotective effect by enhancing the expression of antioxidant enzymes and reducing the expression of genes associated with Alzheimer's disease^[100]. Secondly, polyphenols demonstrate substantial anti-inflammatory effects by restraining the overactivation of microglia and the synthesis and secretion of pro-inflammatory cytokines (IL-1 β and TNF- α), which subsequently hinders the chain reaction associated with chronic neuroinflammation^[101]. Third, some polyphenols, especially ferulic acid, have been shown in experimental studies to interfere with the aggregation process of β -amyloid or inhibit the excessive phosphorylation of tau protein^[102]. The abnormal deposition of these proteins is a core pathological feature of AD. A systematic review and meta-analysis of preclinical studies confirmed that ferulic acid effectively improves spatial memory and reduces A β burden in various rodent AD models^[103]. Notably, the neuroprotective effects of specific polyphenolic compounds exhibit a dose-dependent characteristic. From a clinical application perspective, a systematic review and meta-analysis encompassing 13 studies with a total of 849 participants demonstrated that polyphenol supplementation is significantly associated with global cognitive improvement (pooled mean difference in Mini-Mental State Examination [MMSE] score: 2.06, 95% confidence interval [CI]: 0.62–3.49)^[104]. However, the effects varied among different polyphenol types—flavonoids were associated with modest improvements in MMSE scores, whereas stilbenoids primarily showed benefits in activities of daily living (ADCS-ADL).

Additionally, the polyphenols and their metabolites in WGs may directly act on specific cellular signaling pathways (such as the Nrf2/ARE and PI3K/Akt pathways), activating the endogenous antioxidant defense system and enhancing the survival capacity of neurons^[105]. Whole grain intake is closely associated with positive changes in gut microbiota composition. Polyphenolic compounds and their microbial metabolites (such as SCFAs) may indirectly exert anti-inflammatory and neuroprotective effects by regulating bidirectional communication along the gut-brain axis^[106].

4.5 Modulation of the immune system

The human immune system comprises both innate and adaptive immunity, which function in tandem. The innate immune system includes physical barriers (such as skin and mucous membranes), immune cells (including macrophages, neutrophils, NK cells, and dendritic cells), and soluble factors (complement, antimicrobial peptides, and cytokines). It rapidly detects pathogens through pattern recognition receptors and

initiates an immediate defense response. Adaptive immunity is a precise and persistent specific defense mechanism based on B lymphocytes and T lymphocytes^[107]. Additionally, the intestine can play a central role in regulating immune homeostasis as an immune organ. Effective immune modulation is a crucial approach for treating immune-related diseases, such as cancer, inflammation, intestinal diseases, and asthma^[108]. The immune system's function is highly dependent on the integrity of its cells and is susceptible to damage from oxidative stress.

Polyphenols are essential for the immune system, as they help to modulate the function of immune cells and the body's inflammatory responses. Animal experiments have provided direct evidence for the immunomodulatory effects of whole-grain-derived polyphenols. In a controlled dietary intervention, mice fed for five weeks with four different polyphenol-rich cereal fractions (wheat germ, buckwheat flour, fine rice bran, and wheat middlings) exhibited significant improvements in multiple leukocyte functions, including enhanced chemotaxis capacity, increased microbicidal activity, elevated lymphoproliferative response to mitogens, and altered release of IL-2 and TNF- α , together with an improved antioxidant status characterized by reduced oxidized glutathione and lower lipid oxidative damage^[109].

5 Application of omics technologies in whole-grain fermentation

5.1 Understanding the processes and identifying unknown species

The fermentation process in WGs involves complex dynamics within microbial communities. Traditional methods such as pure culture and single-target assays struggle to elucidate these processes, whereas omics technologies (genomics, transcriptomics, and metabolomics) provide systematic research tools for this purpose (Fig. 6). Genomics reveals the composition and functional potential of microbial communities through high-throughput sequencing and the analysis of all microbial DNA in fermentation substrates. By sequencing the total DNA of whole-grain substrates during the fermentation process, researchers can identify dominant and rare microorganisms at different stages and under different fermentation conditions^[110]. In studies of fermented whole wheat products, 16S rRNA gene sequencing clearly revealed a flora structure centered on *Lactobacillus fermentum*, *Enterococcus faecium*, and *Pediococcus acidilactici*^[111]. Genomics can also predict the functional potential of fermentation microbial communities. Through genome-wide association studies (GWAS), functional genes closely associated with the biosynthesis of flavonoids during sorghum fermentation have been identified, providing targets for the targeted regulation of fermentation microbial communities^[112]. In addition, several fermentation studies have shown that genomics and metabolomics can reveal significant changes in the abundance of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces cerevisiae*, as well as the identification of partially uncultured microbial taxa, such as members of the novel phylum Thick-walled Bacteria^[66].

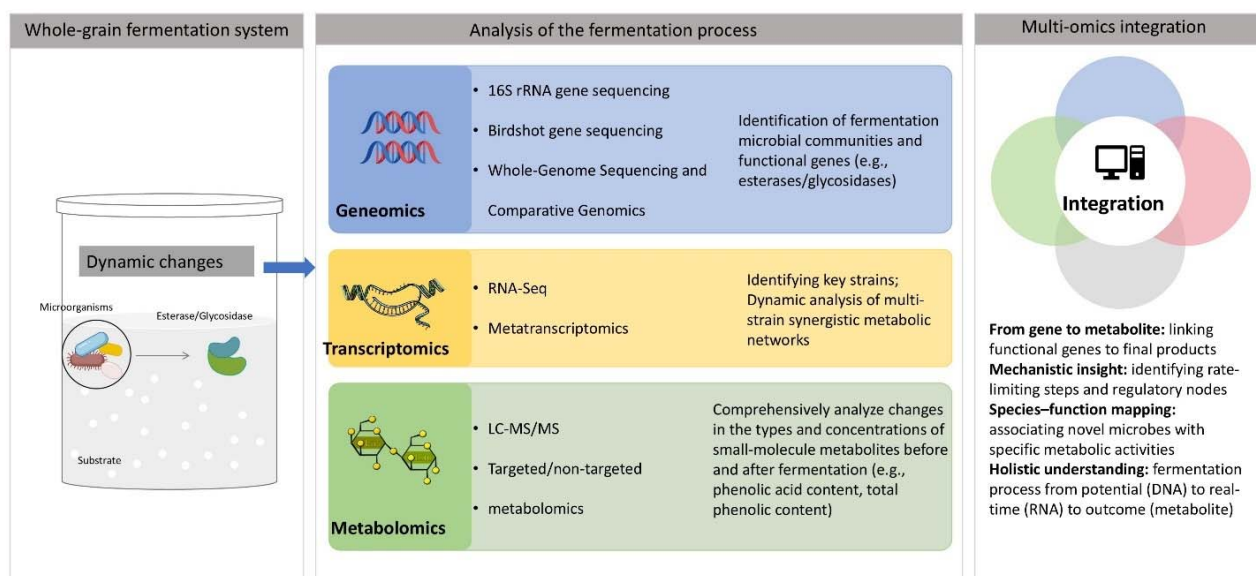


Fig. 6 Application of omics technologies in whole-grain fermentation systems.

Note: LC-MS, Liquid Chromatograph-Mass Spectrometer.

The release of phenolic compounds is closely associated with microbial hydrolytic enzymes such as esterases and glycosidases. Genomics not only provides a powerful tool for identifying the genes encoding these enzymes but also directly addresses key bottlenecks in the phenolic release process. GWAS can link microbial genotypes to their ability to hydrolyze bound phenolic compounds. For example, Cheng et al. performed whole-genome sequencing of *Lactobacillus plantarum* dy-1 and identified a sulfatase gene from the CAZy database; subsequent studies demonstrated that this enzyme can hydrolyze the ester bond between phenolic acids and polysaccharides^[113]. A key limitation of GWAS is their reliance on culturable strains and large sample sizes, which precludes the majority of unculturable or rare microorganisms in whole-grain fermentation ecosystems. Single-cell genomics and metagenomics enable functional gene retrieval from unculturable taxa without prior cultivation. For instance, metagenomic screening of the human gut microbiota during in vitro fermentation of whole wheat bran successfully identified multiple novel feruloyl esterase genes^[66]. These complementary genomic strategies facilitate the rational design of synthetic microbial consortia with synergistic hydrolytic functions for whole-grain fermentation. Recent evidence indicates that LAB (e.g., *Lactobacillus johnsonii*, *L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. brevis*, and *L. fermentum*) transform grain polyphenols via decarboxylation, reduction, demethylation, and hydrolysis, suggesting that combining strains with complementary metabolic pathways could enhance total phenolic release^[114]. Nevertheless, experimental validation of such consortia specifically designed for whole-grain fermentation remains nascent. Major challenges include alleviating cross-inhibition, managing substrate competition, and synchronizing temporal expression patterns of secreted enzymes.

Transcriptomics further addresses bottlenecks related to temporal and environmental regulation by revealing when and under which conditions key enzyme-encoding genes are actively expressed. RNA-Seq-based analyses allow the identification of transcriptionally active pathways involved in phenolic metabolism, thereby guiding the optimization of fermentation parameters (e.g., pH, temperature, and

substrate composition) to enhance enzyme activity and phenolic release^[115]. Nevertheless, transcriptomic data are often difficult to directly translate into functional outcomes due to post-transcriptional regulation. Finally, metabolomics complements these approaches by linking microbial activity to changes in phenolic profiles. In the fermentation of corn seeds (*Zea mays* L.), UPLC-DAD-based metabolomics analysis revealed that phenolic compounds, including anthocyanins and caffeic acid, inhibited the proliferation of pathogenic bacteria by promoting the growth of LAB^[116].

5.2 Mass spectrometry-based metabolomics for detecting microbial metabolites

Metabolomics, particularly through advanced mass spectrometry (MS) techniques, is crucial for characterizing the chemical consequences of whole grain fermentation. High-resolution mass spectrometry (HRMS) is an indispensable tool for untargeted analysis. It offers high-precision mass measurements with an error margin of less than 5 ppm, enabling the inference of identities for thousands of metabolites, including novel phenolic derivatives, lipids, and peptides, based on their exact masses and isotope patterns^[117]. HRMS has significantly contributed to the discovery of 110 phenolic compounds in sorghum and 159 flavonoid compounds in rice^[118]. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the standard method for the quantitative analysis of key metabolites, including specific phenolic acids, ferulic acid, alkylphenols, and short-chain fatty acids, utilizing multiple reaction monitoring or selected reaction monitoring modes^[119]. Gas chromatography-mass spectrometry (GC-MS) plays a crucial role in understanding energy metabolism and flavor formation during the fermentation process. MS-based metabolomics technology offers significant advantages in elucidating the dynamics of microbial metabolites in fermented WGs. It is adept at accurately tracing the transformation pathways of key functional factors, such as phenolic acids. One study employed LC-MS/MS to quantify free, bound, and conjugated phenolic acids in whole wheat and rye sourdoughs, revealing that *Lactobacillus plantarum* specifically metabolizes free ferulic acid, while *L. hammesii* hydrolyzes bound ferulic acid through esterase activity, thereby significantly enhancing its bioavailability^[55].

5.3 Synergistic integration of multi-omics data

The actual value of omics technologies lies in the integration of genomics, transcriptomics, proteomics, and metabolomics data. This approach provides a holistic understanding that transcends the sum of individual omics data. The integrated analysis of metabolomics and genomics has revealed a correlation between the alleles of bHLH transcription factors in rice and the characteristics of a low glycemic index^[120]. Similarly, combined metabolomic and transcriptomic analyses in wheat fermentation studies have elucidated the molecular mechanisms by which the TaMYB10 and TaMYC1 genes regulate anthocyanin synthesis^[121]. Notably, UDP-glucuronosyltransferase genes have demonstrated a strong correlation with antioxidant flavonoid synthesis pathways through the integration of metabolomic and genomic data in millet fermentation^[122]. Multi-omics technologies have played a crucial role in elucidating the mechanisms underlying fermentation enhancement. Researchers utilized multi-omics data integration to discover that microbial secretion of *Rhizopus* enzymes released bound phenolic compounds, resulting in a 64.4% increase

in free phenols^[123]. Moreover, genomics identified the upregulation of microbial esterase genes, proteomics validated increased ferulic acid esterase activity, and metabolomics detected the accumulation of free phenols, including ferulic acid and p-coumaric acid.

6 Conclusion and Future perspectives

The fermentation of WGs markedly enhances the release, transformation, and bioaccessibility of phenolic compounds through the enzymatic activities of microorganisms, including LAB, yeasts, and filamentous fungi. These microbial processes improve the nutritional and functional properties of WGs, as evidenced by increased total and free phenolic contents and the liberation of bound phenolics (e.g., ferulic acid).

Although phenolic-rich WGs and their extracted phenolic fractions have been extensively associated with various health benefits—such as modulation of lipid and glucose metabolism, improvement of gut health, neuroprotection, and immune regulation—direct evidence specifically derived from fermented WGs remains limited. Current understanding of their health effects is therefore largely extrapolated from studies on phenolic-rich grains or isolated phenolic compounds, rather than from fermented WG matrices *per se*. This gap necessitates cautious interpretation when linking fermentation-induced alterations in phenolic profiles to physiological outcomes.

Despite these advances, the current understanding of WG fermentation is constrained by several limitations, including the lack of standardized fermentation protocols, variability in microbial strains, and the structural complexity of grain matrices. In addition, the exploration of WG-derived bioactive compounds remains insufficient, particularly with respect to the identification of novel phenolic derivatives generated during fermentation and the elucidation of their functional relevance. Although fermentation is widely recognized to enhance phenolic bioaccessibility, the mechanisms underlying their release from complex cell wall matrices, as well as their subsequent absorption, metabolic transformation, and systemic distribution in humans, remain poorly understood.

Moreover, the specific roles of different microorganisms in phenolic release and transformation have not been fully elucidated. Existing evidence suggests that enzyme-mediated processes—such as the activities of feruloyl esterases, glycosidases, and other carbohydrate-degrading enzymes—play critical roles. However, quantitative characterization of these enzymatic activities, their synergistic interactions, and regulatory mechanisms is still lacking. The absence of standardized evaluation frameworks and unified biomarkers further hampers cross-study comparisons. Furthermore, most available evidence is derived from *in vitro* and animal studies, with a notable scarcity of well-designed human intervention trials focusing specifically on fermented WGs.

Future research should therefore prioritize: (i) the screening and domestication of microbial strains with high enzymatic activity, specificity, and stability, supported by quantitative enzyme assays; (ii) systematic investigation of mixed-culture fermentation systems, with emphasis on their synergistic effects on phenolic release, transformation, and bioaccessibility; and (iii) the integration of multi-omics approaches (e.g.,

genomics, transcriptomics, and metabolomics) to quantitatively elucidate microbial interactions, enzymatic networks, and metabolic pathways. Importantly, more rigorously designed studies—particularly human intervention trials—are urgently needed to directly evaluate the health effects of fermented WGs as complex food matrices, rather than relying on evidence from phenolic-rich grains or isolated compounds, thereby enabling a more accurate assessment of their physiological relevance and functional potential.

Data availability

No data was used for the research described in the article.

Conflict of interest

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

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