

Review

A Review on Modeling the Fermentation Process of Dairy Products Using Multi-Omics and Artificial Intelligence Approaches

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Abstract

In dairy production, the fermentation process is a complex biochemical system that plays a significant role in determining the quality criteria of the final product. Traditional methods for controlling fermentation rely on limited and non-standard process parameters. In recent years, omics technologies have come to the forefront, enabling the monitoring of fermentation dynamics at the molecular level with their current, efficient, and reliable approaches. Thanks to omics approaches such as metabolomics, metagenomics, proteomics, and lipidomics, starter culture behavior, metabolite formation, aroma–texture formation, and microbial interactions in the fermentation process can be characterized more comprehensively. On the other hand, evaluating or calculating high-dimensional omics data using traditional statistical methods presents a challenge. Artificial intelligence applications are overcoming this challenge, offering significant opportunities for the accurate and reliable evaluation of data. Artificial intelligence-powered models hold promise in areas such as predicting fermentation kinetics, process control, optimizing quality criteria, and revealing the therapeutic potential of products through metabolites. This compilation aims to comprehensively address current approaches to modeling the fermentation process and quality parameters of dairy products using multi-omics technologies and artificial intelligence applications. In this respect, it will provide current and important perspectives for industrial applications and future studies.

Keywords: fermented dairy products; multi-omics technologies; artificial intelligence; multi-omics data integration

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1. Introduction

Fermented foods, an indispensable part of humanity's diet, have always attracted interest. However, nowadays, with consumers becoming more aware of healthy living, interest in fermented products has increased even more [1]. Fermentation is a fundamental biotechnological process that has been used for centuries to preserve foods, create new flavors, and impart health benefits by harnessing the metabolic activities of microorganisms [2]. In fermentation, a fundamental biochemical mechanism in which substrates are converted into cellular energy, biomass, and metabolites by microorganisms, the overall quality of the final product is largely shaped by these metabolites that are released [3].

In all traditional or modern biotechnological processes, the success of fermentation is directly dependent on the quality of the substrate used. Milk, with its high protein content

and rich nutritional value, is a valuable food for these systems. The rich nutritional matrix of milk plays a critical role in the optimal development of the microorganisms that carry out fermentation [4,5]. Fermentation is one of the most fundamental biotechnological ways to protect milk and dairy products, which are structurally highly susceptible to spoilage, from microbial spoilage and to safely extend the shelf life of the product. In addition, the fact that the technologies and infrastructure requirements used in milk fermentation processes do not necessitate very high costs makes this method economical and sustainable on an industrial scale [6]. Milk is a rich source of protein, containing amino acids and bioactive peptides essential for human health. When this valuable protein matrix is subjected to lactic acid fermentation, it has been found that the digestibility of the milk is significantly increased compared to the unfermented version, thanks to the enzymatic activities in the process [7].

Fermentation is the process by which probiotic microorganisms ferment prebiotic components, leading to the release of postbiotic metabolites that have positive effects on health [4]. The symbiotic interaction mechanism between probiotics and prebiotics enhances the bioavailability of these components in the gastrointestinal system, thereby improving the health benefits offered by the final product [8]. Postbiotics repair the epithelial tissue in the gut and regulate immune metabolism. It also exhibits anti-inflammatory, antioxidant, and antitumor properties [9].

Fermented dairy products, whose most popular examples in food science and nutrition literature include yogurt, kefir, fermented milk, sour cream, and specific types of cheese, provide critical improvements in human physiology when consumed as part of the diet. In this context, it is emphasized that regular consumption of these products offers multifaceted and holistic benefits to human health through mechanisms such as significantly increasing the feeling of satiety in individuals, improving overall gut health by optimizing gastrointestinal functions, contributing to the improvement of insulin sensitivity (one of the metabolic imbalances), and regulating lipid metabolism [4,10].

Accordingly, this review provided the biological basis of milk fermentation, the generation of molecular information through omics technologies, strategies for integrating heterogeneous multi-omics datasets, and ultimately, artificial intelligence-based predictive models in the evaluation of multi-omics data. Furthermore, by highlighting explainable artificial intelligence approaches that enhance the interpretability of artificial intelligence models, it presented strategies and current challenges for optimizing milk fermentation dynamics as a narrative literature review with future perspectives. While searching for relevant studies, databases such as Web of Science, Scopus, and PubMed were utilized, and searches were conducted using keyword groups such as “dairy fermentation,” “fermentation dynamics,” “multiomics approaches,” “metabolomics,” “metagenomics,” “transcriptomics,” “proteomics,” “multiomics data integration,” “machine learning,” “deep learning,” “explainable artificial intelligence,” and “digital twin.”

2. Microbiological Basis of Milk Fermentation

It is known that the main driving force in milk fermentation is the metabolic activity of microorganisms, and that this activity leads to various biochemical processes, including the conversion of carbohydrates, proteins, and lipids into various metabolites. Furthermore, these activities shape the product's quality, nutritional value, safety, and functional properties. Therefore, understanding the microbial communities underlying milk fermentation is the first step in unraveling the molecular mechanisms involved in this biochemical process.

The successful and standardized production of fermentative food products requires the use of specific starter cultures to guide the process. When selecting starter cultures

to be integrated into industrial processes, technological factors such as safety for human consumption, acidification rate that accelerates the process by lowering the pH of the environment, and exopolysaccharide (EPS) production capacity that improves the structural properties of the final product are of great importance [11].

Another technologically important parameter in the selection process of starter cultures is galactose metabolism. The accumulation of galactose in the final product is absolutely undesirable from both the producer and consumer perspectives, as it can cause sensory defects; therefore, it is essential for maintaining product quality that the preferred microorganisms successfully metabolize and consume galactose in the reaction chain [12].

The vast majority of strains used industrially in dairy fermentation are classified under the lactic acid bacteria (LAB) group. Essentially defined as Gram-positive (+) non-spore-forming microorganisms that convert glucose into lactic acid through fermentation, the LAB group plays a crucial role in enhancing the specific aroma, structural properties, and overall final quality of milk. Although these bacteria can be found as a natural flora element in the matrix of some traditional dairy products, they are usually introduced into the process externally in the form of starter cultures to ensure industrial production standards. The species historically classified under the genus *Lactobacillus*, and now divided into various new genera, constitute the largest taxonomic division of the LAB group, followed by the genera *Streptococcus* and *Lactococcus*, which are of great importance in dairy technology [6,13–15].

In fermentation processes applied in the past, when microbiological dynamics were not fully understood, environmental temperature conditions were the primary parameter guiding microorganism growth. As an adaptation process dependent on optimum growth temperature, it has been observed that thermophilic (30–45 °C) LAB strains become dominant in countries with high ambient temperatures, while mesophilic (20–30 °C) LAB strains develop in countries in cold climate zones. This regional temperature difference and the resulting changes in microbial flora lead to differentiation in the metabolites produced by bacteria, thus creating a basis for structural changes in the sensory properties and characteristic taste of the final product [6,16]. As part of their metabolic activities, the LAB group hydrolyzes proteins, lipids, and carbohydrates in the environment using their specific enzymes. As a result of these reactions, these macromolecules are broken down into peptides, free amino acids, free fatty acids, and lactic acid, reducing them to subunits with high physiological digestibility [1]. The metabolic pathways of milk components and their effect on product quality are presented in Figure 1.

LAB, which is divided into two main classes, homofermentative and heterofermentative, according to its metabolic pathways, differs in terms of its end-product profiles. The homofermentative group, which includes genera such as *Pediococcus*, *Streptococcus*, and *Lactococcus*, produces only lactic acid as the primary metabolite as a result of glucose fermentation. In contrast, the heterofermentative group, which includes genera such as *Weissella* and *Leuconostoc*, metabolizes glucose, releasing lactate as well as ethanol and carbon dioxide (CO₂) [6].

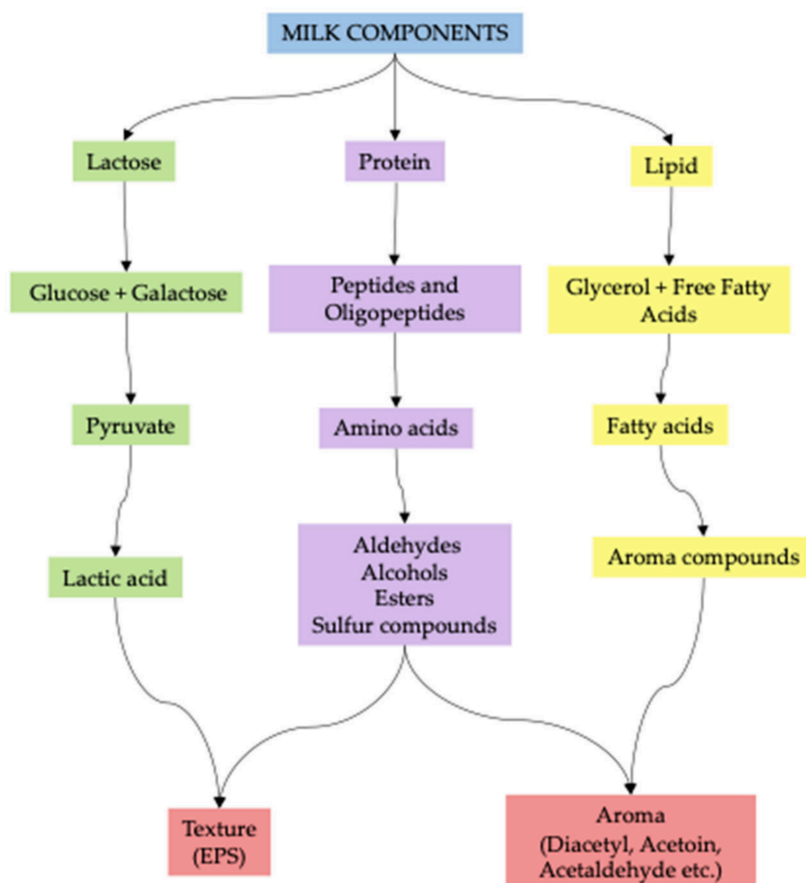


Figure 1. Metabolic pathways of milk components: key metabolites and their impact on product quality [12,17–19].

Fermented milk production is based on the principle that the selected culture lowers the pH of the milk, causing coagulation, or increases its acidity without causing coagulation. With increasing acidity, microorganisms other than the LAB group in the environment undergo competitive inhibition due to low pH and organic acid accumulation, and lose their viability. Differences in the characteristics of the selected strains, such as the number of live cells and fermentation time, cause changes not only in the taste and aroma characteristics of the fermented milk but also in its metabolites [4,20].

2.1. Aroma and Texture Development

The aroma-related activities of LABs are species-dependent, and some specific activities are found only in a small number of species. An example of this is the fact that branched-chain α -keto acid decarboxylase activity, which enables the formation of malt-like branched-chain aldehydes from branched-chain amino acids, is found only in *Lactococcus lactis*. These bacteria also play an active role in the formation of diacetyl and acetoin, which are specific aroma compounds. Branched-chain α -keto acid decarboxylase activity was not detected in the *Lactobacillus* and *Leuconostoc* strains examined. However, diacetyl, acetic acid, and ethanol production increases depending on the genus *Leuconostoc* [21,22]. The bacteria *Propionibacterium freudenreichii* subsp. *shermanii* and *Brevibacterium linens*, which are prominent for creating the specific cheese aroma, also play an active role in cheese texture (structural properties) [23].

The formation of aroma in fermented dairy products is essentially a complex, multi-factorial process, rather than the result of a single microbial species or metabolic pathway. Here, carbohydrate metabolism provides central intermediates such as pyruvate, as well as

organic acids, while proteolysis contributes by converting the resulting peptides and free amino acids into various compounds such as aldehydes, alcohols, and other volatile compounds. Furthermore, lipolysis, through the production of free fatty acids that contribute to direct aroma or as precursors to other volatile compounds, also contributes to this process. The relative contribution of these metabolic pathways depends on many factors, including microbial composition, strain-specific enzymatic activity, inter-microorganism interactions, and fermentation conditions. Ultimately, the aroma profile in fermented dairy products is a process that represents a dynamic metabolic phenotype and is framed by the coordinated transformation of multiple substrates [24–26]. On the other hand, Han et al. [27], who associated changes in aroma compounds during yogurt fermentation with metabolic pathways such as pyruvate metabolism, amino acid metabolism, and tricarboxylic acid cycling, have demonstrated the importance and contribution of omics-based studies in understanding this complex process.

In addition to aroma development, the improvement of texture in fermented dairy products also depends on metabolic activity. In the production of yogurt and fermented milk, microorganisms such as *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* are generally preferred [28]. Although both *L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus* are capable of synthesizing EPS in traditional yogurt, *S. thermophilus* is more frequently preferred industrially due to its proliferation in the early stages of fermentation [29]. The goal is for the yogurt produced through the symbiotic relationship between these two microorganisms to contain at least 10^7 CFU/g of live culture. Yogurt may contain active β -galactosidase located in the cytoplasm of live bacteria, as well as active and free lactase released by dead bacteria; these components contribute to lactose digestion [30]. *L. delbrueckii* subsp. *bulgaricus*, a significant industrial representative of the LAB group, is a strain that provides high yields by using lactose as a primary energy source under anaerobic conditions. This microorganism, which stands out in milk technology with its advanced lactose catabolism and high EPS production, also directly enriches the aroma profile and sensory quality of the final product by breaking down casein with its strong proteolytic activity [15,31,32].

In fermented dairy products, texture develops around a network of biochemical, microbial, and physicochemical processes. Acidification progressively destabilizes casein micelles, promoting protein gel network formation, while proteolysis alters the protein matrix, affecting its structural organization and stiffness. Furthermore, depending on their molecular structure, concentration, location, and interactions with other compounds, microbial exopolysaccharides can alter viscosity, water retention, syneresis, and rheological behavior. On the other hand, texture formation in fermented milk products cannot be attributed solely to acidification and EPS production; starter culture, proteolytic activity, fermentation kinetics, and milk matrix are the primary factors involved [29,33,34]. Here, omics approaches prove significantly useful in exploring the relationships between microbial metabolic activities and textural properties. Indeed, the relationship between yogurt firmness, flow behavior, and syneresis with fermentation metabolites, as well as the connections between microbial metabolic, rheological properties, and aroma formation in fermented milk, have been elucidated through omics approaches [35,36].

From a functional perspective, starter cultures also impart various bioactive properties to the product. The addition of certain microorganisms such as *Lactocaseibacillus paracasei* and *Lactiplantibacillus plantarum* results in the formation of antioxidant peptides through fermentation [37,38]. The selection of starter cultures in cheese production is important in terms of proteolytic activity and the formation of bioactive metabolites and peptides [11]. In yogurt production, the addition of *Bifidobacterium* has a multifaceted effect on fermentation kinetics. This method maximizes the viability rate of the existing microorganisms and accel-

erates the acidification process, significantly shortening the targeted fermentation time [39]. *Lactobacillus acidophilus* and *Bifidobacterium animalis* subsp. *lactis*, the most commonly preferred microorganisms as probiotics, exhibit high pH stability during fermentation and subsequent processes. Their stable biochemical structure helps them maintain their viability during cold storage and allows them to offer a balanced acidity and sensory development in the final product [40,41].

The functional properties of fermented dairy products are also shaped by the simultaneous transformation of proteins, lipids, carbohydrates, and microbial metabolites. The formation of biologically active peptides with potential antioxidant, antimicrobial, antihypertensive, etc. properties occurs through proteolysis. Fermentation-derived metabolites, such as microbial EPSs, can contribute to techno-functional and physiological functionality. Ultimately, the functional potential of fermented milk products is characterized not only by the presence of probiotic microorganisms but also by the metabolites and molecules formed as a result of their growth and interaction with the milk matrix. As with other features, the use of omics approaches here offers important insights into understanding these metabolic processes. While proteomic or peptidomics approaches are prominent in the characterization of milk proteins and bioactive peptides, metabolomic approaches are gaining prominence in the discovery of low molecular weight metabolites associated with functional properties. For example, one study correlated techno-functional properties in fermented goat yogurt with fermentation-derived metabolite profiles via metabolomic approaches, while other studies demonstrated the potential functionality of fermented dairy products through multi-omics approaches [35,42,43]. Indeed, Awwad et al. [44] used a combination of LC-MS quadrupole time-flight metabolomics method and machine learning to predict various potential biological activities and functional properties of fermented milk, such as antioxidant, antihypertensive and anticancer activity.

2.2. Fermentation Metabolites and Basic Biochemical Transformations

2.2.1. Carbohydrate Metabolism & Organic Acid Dynamics

Lactose, the main carbon source in milk, is a disaccharide formed by the combination of α/β -D-glucose and β -D-galactose molecules. Milk fermentation is fundamentally based on the mechanism of converting lactose into lactic acid; as a result of the reactions, lactic acid is released as the main product, while acetic acid is synthesized as a secondary metabolite accompanying the process [12,19]. During lactic acid fermentation, not all of the lactose in the milk matrix is consumed; only about 20% of the initial total lactose is broken down and metabolized by microbial activity [45]. Milk fermentation involves three pathways: glycolysis (breakdown of sugar), proteolysis (breakdown of proteins), and lipolysis (breakdown of fats). The products resulting from lactose and protein metabolism constitute the flavor mechanism of yogurt [17].

Lactose is transported across the cell membrane via the lactose permease system or the phosphoenolpyruvate-dependent phosphotransferase system (Lac PEP-PTS). Depending on the transport mechanism, lactose taken into the cell and galactose released can be metabolized via two different pathways. Unphosphorylated lactose (Lac permease), which enters the cell via the permease system, is hydrolyzed into free glucose and galactose by β -galactosidase, while phosphorylated lactose is broken down into glucose and galactose-6-phosphate by phospho- β -galactosidase. Free glucose enters the glycolytic Embden–Meyerhof–Parnas (EMP) pathway. Free galactose is converted to glucose-1-phosphate, the end product of the Leloir pathway, and participates in the EMP pathway; while galactose-6-phosphate is converted to triose-3-phosphates (glyceraldehyde-3-phosphate (G3P) & dihydroxyacetone phosphate (DHAP)) via the tagatose pathway. The end product of all these pathways is lactic acid, which is obtained from pyruvate by

lactate dehydrogenase. As the amount of lactic acid increases, the acidity of the product increases, and consequently, the pH decreases. At low pH levels, the β -galactosidase enzyme becomes inactive, preventing further breakdown of lactose and halting fermentation [12,17,19,20,31,40]. Although lactose is broken down through fermentation, it can still be found in fermented dairy products in amounts of 4–5% [45]. The lactose to lactic acid conversion pathway is presented in Figure 2.

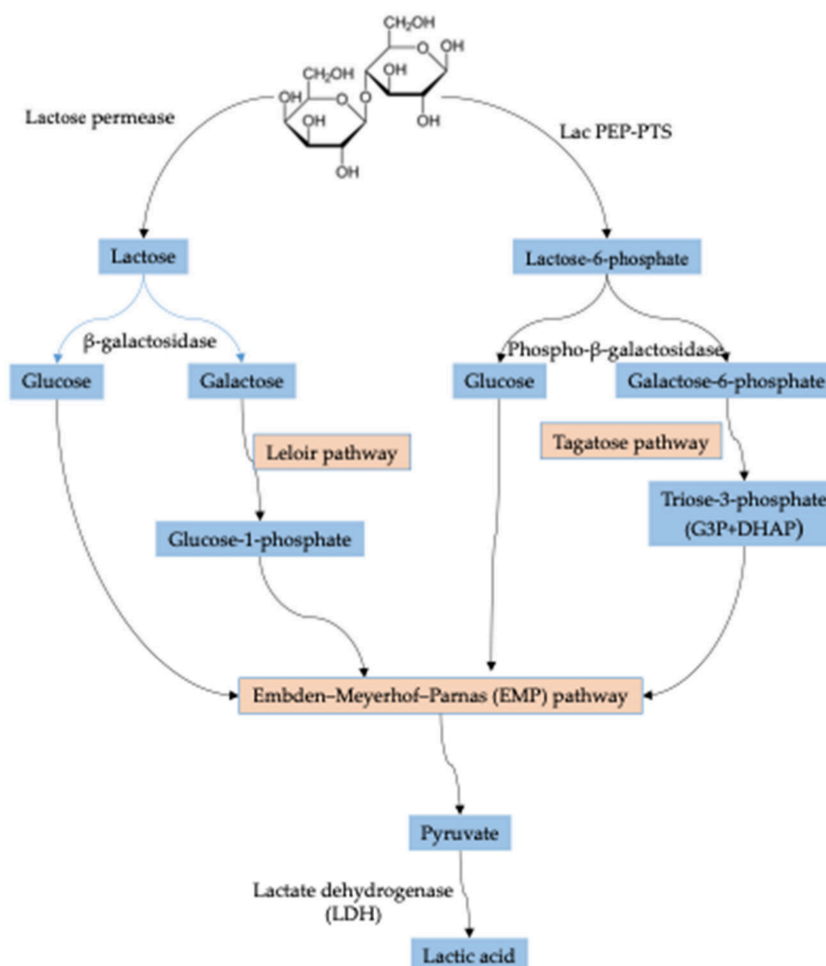


Figure 2. Lactose to lactic acid conversion pathway [12,17,19,20,31,40].

In the synthesis process of acetaldehyde, the refreshing component that gives yogurt its nutty or apple flavor, pyruvate is first decarboxylated by the PDH (pyruvate dehydrogenase) enzyme to convert it into acetyl-CoA molecules. Acetyl-CoA molecules are reduced to acetaldehyde by the enzyme ACDH (acetaldehyde dehydrogenase) [22,38]. Pyruvate is obtained not only from lactose but also from citric acid in the environment via oxaloacetate by the OAD (oxaloacetate decarboxylase) enzyme. The resulting pyruvate is converted into acetoin or diacetyl, the main flavor components, by the enzymes α -acetolactate synthase (ALS) and α -acetolactate decarboxylase (ALDB). In the first step of the reaction sequence, pyruvate molecules are converted into α -acetolactate, a critical intermediate metabolite, primarily catalyzed by the ALS enzyme. After this stage, metabolic pathways branch off into two. A significant portion of α -acetolactate is decarboxylated by the ALDB enzyme through a series of enzymatic reactions to convert it into the target metabolite, acetoin. The remaining portion is directly converted to diacetyl via a non-enzymatic oxidative decarboxylation (NOD) mechanism [22,38,46,47].

2.2.2. Proteolysis & Bioactive Peptide Generation

The LAB group breaks down milk proteins into peptides and oligopeptides using proteinase enzymes. The resulting smaller structures are transported into the cell via transport systems (oligopeptide transporters (Opp) and di-/tripeptide transporters (Dpp, DtpP, and DtpT)) and converted into free amino acids by specific peptidase enzymes. These free amino acids are converted into various alcohols, aldehydes, acids, esters, and sulfur compounds, leading to the development of specific flavors in dairy products [17,48].

2.2.3. Lipolysis & Volatile Aroma Compound Synthesis

The process by which milk lipids are broken down through enzymatic reactions is called lipolysis. In the milk matrix, this process can occur spontaneously or induced, and the reactions are catalyzed by lipase enzymes. Lipolysis results in the formation of glycerol and free fatty acids from triglycerides. Although high concentrations of free fatty acids can cause bitter taste defects, lipolysis occurring at controlled levels contributes to flavor development, especially in dairy products such as cheese [49,50]. Intermediate metabolites formed as a result of glycolysis, proteolysis, and lipolysis play a fundamental role in the formation of the characteristic aroma profile of fermented dairy products. More than 90 volatile aroma compounds have been detected in yogurt, while 39 volatile aroma compounds have been reported in kefir and 36 volatile aroma compounds in cheese [18]. Aroma pathways branching from pyruvate are shown in Figure 3.

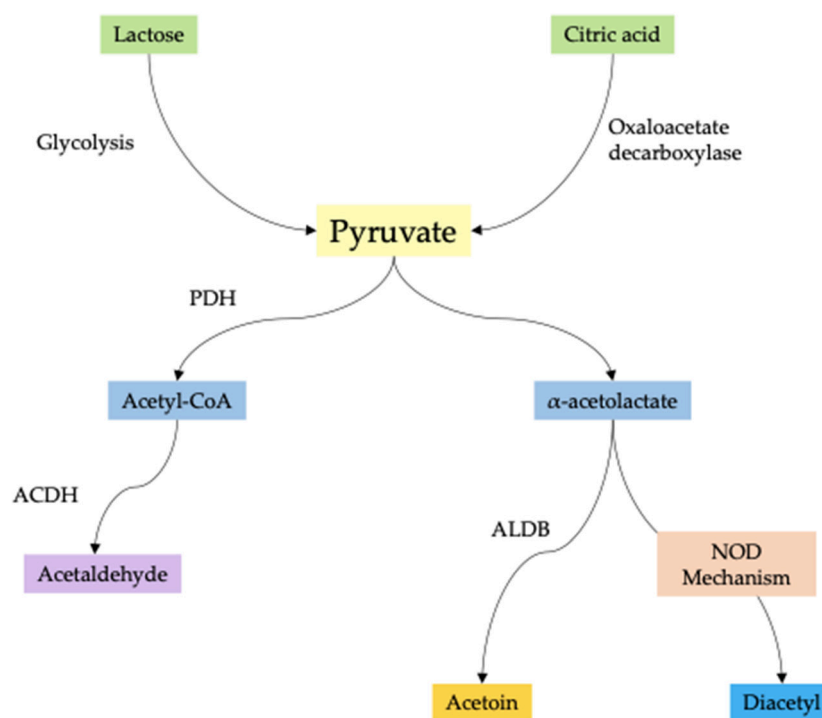


Figure 3. Aroma pathways branching from pyruvate [22,38,46,47].

2.2.4. Functional Microbial Metabolites: EPS and Bacteriocins

EPSs exhibit a wide variety in terms of their molecular properties (structure, mass, size, charge) and rheological characteristics, and are divided into two main groups: HoPS (homopolysaccharides) and HePS (heteropolysaccharides). HoPSs, which are generally synthesized by sourdough-derived LABs, consist of a single monosaccharide unit (glucose or fructose) [29]. It is also known that EPSs, which can be synthesized by some LABs used in commercial yogurt production during the milk fermentation process, play an important

role in microbial ecology as natural biothickeners, biofilm formers, stress tolerants, and cell adhesives within the product [15,51].

LABs not only produce metabolites but also synthesize antimicrobial compounds. The ribosomally synthesized antimicrobial peptides they produce, which inactivate microorganisms, are called bacteriocins [52]. These peptides have the ability to eliminate microorganisms and pathogens that cause microbiological spoilage. Because they are protein in structure, they can be easily broken down and digested by protease enzymes in the human gastrointestinal system. Given this physiological fact, they are considered completely safe and natural biopreservatives for human consumption in the food industry. Temperature, stirring, and pH play important roles in the production of bacteriocins [53]. The autolysis process in LAB cells, induced by bacteriocins and peptidoglycan hydrolases (PGH), is essentially a process of self-destruction. This process results in the complete breakdown of the cellular structure by hydrolyzing the peptidoglycan network, the main component of the cell wall, through the action of autolysins and peptidoglycan hydrolases, which act as endogenous enzymes. This lysis process contributes to aroma development in many ways through the released intracellular enzymes and plays a critical role in processes such as cheese ripening by promoting the breakdown of hydrophobic bitter peptides [21,25].

3. Molecular Data Generation Through Omics Technologies

While traditional approaches to the fermentation process have provided valuable information, they are unfortunately insufficient for a deep understanding of the complex metabolic activities and fermentation dynamics within microbial communities. Here, advances in omics technologies have provided a solution to the scope and understanding of biochemical and molecular changes at the biological level.

Innovative and advanced analytical methods used to characterize the profiles of biological molecules in depth can be defined as omics technologies, while these approaches in the food field are referred to as Foodomics. Foodomics, first defined as a discipline by Alejandro Cifuentes in 2009, is a field of science that considers the quality and safety of fresh or processed foods within the framework of consumer welfare, health, and preferences. Foodomics, representing a combination of omics approaches such as genomics, proteomics, transcriptomics, metabolomics, and lipidomics, offers a fruitful research field by allowing for the detailed examination of the biochemical, cellular, and molecular properties of foods and characterizing the relationships between these properties [54–56]. Additionally, the term nutriomics has recently emerged to examine the relationship between food, human health, and diet at the molecular level. This includes fields such as nutrimetabolomics, nutrigenomics, nutripoteomics, nutritranscriptomics, and nutriepigenetics, which specifically encompass in vitro and in vivo nutrition studies [56].

Metabolomics, an omics approach, is used in the characterization of various microbial metabolites (<1000 Da) during fermentation. In metabolomic fermentation, the starter culture, substrate, microbiota in the system, temperature, and other parameters play a critical role in monitoring changes in the product. Therefore, compared to traditional methods, it offers advantages such as clarifying metabolic pathways, determining metabolite concentrations, identifying metabolites, enabling biomarker selection, and identifying key parameters affecting metabolite formation [57]. Here, a wide variety of compounds, such as amino acids, oligopeptides, carbohydrates, nucleic acids, polyphenols, organic acids, alkaloids, vitamins, and chemical compounds synthesized by a particular organism or cell, are classified as metabolites. Metabolomics approaches, both targeted and non-targeted, are applied for the identification of secondary metabolites, the detection of different metabolic compounds, and the determination of metabolite diversity. Here, targeted metabolomics applications focus on determining the quantity of desired metabolites, while non-targeted

metabolomics approaches are based on the definition and quantification of metabolite profiles [57–60]. In metabolomic analyses, after extracting endogenous metabolites from the sample, the following steps are followed: chromatographic separation, semi- and/or quantitative mass spectral determination/identification, and application of multivariate statistical methods to characterize changes in the metabolic process [61]. Here, metabolites in food can be successfully detected using technologies such as ultraperformance liquid chromatography (UPLC), high-performance liquid chromatography (HPLC), gas chromatography mass spectrometry (GC-MS), capillary electrophoresis mass spectrometry (CE-MS), and nuclear magnetic resonance (NMR) [58,61,62]. Trimigno et al. [63] demonstrated, using a ^1H -NMR metabolomic approach, that lactose and protein are broken down during yogurt fermentation, while the amounts of acetate, lactate, and citrate increase simultaneously. It was also emphasized that *Lactobacillus* does not produce formate, which it needs for its growth, while *Streptococcus* can produce formate from pyruvate, thus highlighting the importance of the symbiotic relationship between the two strains. Rehman et al. [35] investigated the GC-MS-based metabolite profile in yogurts produced from the milk of a goat breed native to India using multivariate data analysis and regression models. They reported that 102 metabolites were identified in yogurt samples using metabolomic analysis; a clear distinction was made between groups using principal component analysis, and various correlations were determined using correlation heat mapping. Through regression analysis, researchers also revealed the relationships between various metabolites and techno-functional properties.

Genomic applications are used to facilitate the identification and characterization of microorganisms in the fermentation process, and to elucidate the genetic functions of microorganisms and their contributions to the product [64]. Datasets in genomic approaches provide fully sequenced genomes from bacteria that have been studied in detail (e.g., many LAB species). Thus, prototype genomes of the desired strain can be easily generated using these datasets as a reference. Therefore, examining only the genomes may be sufficient to obtain information about all the characteristics of microorganisms [65]. Although various strains differ in genome size and coding, genomic analysis can characterize common genes involved in metabolic processes. Furthermore, these are genes that encode enzymes involved in metabolic processes such as amino acid metabolism, lactic acid production, or the formation of aroma compounds [66]. On the other hand, the genomic information of a previously unstudied microorganism can also be estimated from scratch using computational methods, without relying on an existing gene database. Here, information about characteristic motifs in the DNA sequence, such as promoters, Shine-Dalgarno sequences, and transcription factor binding sites, allows for the identification of genes in previously unidentified genomes through bioinformatic transcription [65]. In genomic fermented products, monitoring microbial dynamics at different stages of the process makes it possible to characterize product quality and spoilage factors. Thanks to advanced techniques and databases, it simplifies the control of fermentation by eliminating the disadvantages of traditional methods such as time, labor, and cost [67]. Liu et al. [68] reported that functional genomic analysis of 227 *Lactococcus lactis* subsp. *lactis* strains isolated from fermented milk products revealed that differentiation events for genes responsible for carbohydrate utilization and lactic acid production resulted in strong lineage-specific selection. In genome-wide association results, researchers determined that single nucleic acid polymorphic loci associated with the *pepF* and *CoiA* genes have a strong association with fermentation ability, thus creating a rapid screening model for potential starter cultures.

First used by Marc Wilkins in 1996, “proteomics” is an omics approach that provides information about the structures, functions, dynamics, and interactions of proteins in a biological system. The complete set of proteins produced by a cell, tissue, or organism over

a specific period is referred to as the proteome. Proteomics is divided into six branches: functional proteomics, expression proteomics, protein–protein interaction studies, post-translational modification analysis, structural proteomics, and proteome mining [69]. Ortea et al. [70] classified proteomics as qualitative, quantitative, and functional proteomics based on their overall purpose. (1) Qualitative proteomics: This refers to the identification and characterization of all proteins in a sample. Here, while it is possible to focus on all the proteins in the sample, i.e., the proteome, subsets of proteins such as sarcoplasmic proteins, glycosylated proteins, and gluten proteins can also be characterized. (2) Differential/Quantitative Proteomics: In food proteomes, the relative amount of proteins can be affected by food composition, technological processes, and the biological interactions of the components. (3) Functional Proteomics: This section describes the functional interactions between proteins or between proteins and other molecules, and the results of these interactions [70]. In recent years, comprehensive characterization of proteins in complex matrices such as foods has been facilitated by advances in various protein separation techniques such as liquid chromatography, two-dimensional polyacrylamide gel electrophoresis, and isotope-coded affinity labeling (ICAT), in addition to recent developments in mass spectrometry and database searches. Here, protein characterization is crucial for examining composition, identifying indicators for quality and adulteration, characterizing the effects of processes such as processing and storage on proteins, and identifying food allergens and novel bioactive components [71]. In the proteomic optimization of fermentation, microorganisms with specific enzymatic activities that characterize numerous proteins and are responsible for shaping the characteristic taste, texture, and aroma of the fermented product should be considered first. Furthermore, various factors such as metabolic activity, stress, competing microorganisms, or chemical substances can alter the quality and activity of proteins here [71]. In one study, a chromatography–electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS)-based method was applied for the proteomic characterization of pathogenic *Enterococcus* from different milk and fermented milk products. The study identified 1403 non-repeating peptides representing 1327 proteins, 310 of which contained proteins directly related to virulence factors for *Enterococcus* pathogenicity. The researchers have submitted the data to the ProteomeX-change database under the identifier PXD036435 for use in research on pathogenic *Enterococcus* species [72]. Chen et al. [73] applied a tandem mass tags (TMT)-labeled proteomic approach to identify differentially expressed proteins in fermented goat milk and determine their relationship with ACE inhibitor activity. ACE inhibitor activity was observed to significantly increase during the 0–16 h portion of fermentation, while it tended to remain stable during the 16–32 h portion. According to proteomic analysis, casein transport was active in the 0–16 h period, while peptidase was active in the 16–32 h period. It was stated that 525 proteins were identified during the fermentation period, and there were significant differences in the proteins identified between 0 h of fermentation and 16 h of fermentation. Furthermore, it was reported that 58 differentially expressed proteins were detected during the 0–16 h portion of fermentation, with 23 of them being upregulated and 35 being downregulated. Furthermore, it was observed that intracellular peptidases of lactic acid bacteria form a complex protein–protein interaction network within a 16–32 h period. Zhang et al. [74] investigated the response of *L. plantarum* NMGL2 in fermented milk to cold and acid stress during a 21-day storage period at 4 °C. Of the differentially expressed proteins identified, 20 were found to be low-temperature-resistant proteins, while 10 were observed to be acid-resistant proteins. Furthermore, *L. plantarum* NMGL2 has been reported to respond to stress conditions through metabolic pathways such as abundant extracellular production of glycolipids and glycoproteins, increased biosynthesis of cell wall components,

increased F1Fo-ATPase expression, increased conversion of cell repair-related proteins and chaperones into appropriate proteins, and activation of the glutamate acid removal system.

In short, the omics approach used to understand the expression of various gene types under different conditions is defined as transcriptomics. The transcriptome is defined as the complete set of RNA transcripts produced by the genome in an organism, which encodes information in DNA and links phenotypes [75,76]. The transcriptome primarily comprises coding mRNAs, but it also includes ribosomal rRNAs, transfer tRNAs, and sRNAs. mRNAs are highly important because they are effective in characterizing the molecular components and functional factors of cells [77]. The transcriptome is characterized by the stages of identifying all transcripts, elucidating the transcriptional structures of genes, and ultimately quantifying the different expression levels of transcripts under different conditions [78]. In the transcriptomic approach, techniques such as real-time reverse transcription (RT)-PCR, microarray, expression sequence tags technology (EST), next-generation RNA sequencing (RNA-seq.), massively parallel signature sequencing (MPSS), and serial analysis of gene expression (SAGE) are used, with RNA sequencing and microarrays being frequently preferred. In microarray methods, the abundance of a pre-determined transcript cluster is measured based on the level of binding to complementary nucleotide probes by hybridization. In RNA sequencing techniques, all transcript RNAs are converted to cDNA and then identified using a high-throughput sequencing method [79]. Sun et al. [80] investigated the biofilm characterization of *L. plantarum* J26 from 79 LAB isolated from fermented milk products, based on its strong biofilm-forming ability, and also examined the metabolic pathway based on transcriptomic sequencing using real-time RT-PCR. In transcriptomic sequencing, differentially expressed genes (DEGs) have been reported to be involved in pathways such as pyrimidine metabolism, glycerol metabolism, and stress response through analyses from Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG). Transcriptomic analyses conducted during the fermentation stages of milk produced with *S. salivarius* ssp. *thermophilus* Snew have shown that DEGs are screened in various categories such as proteins, carbohydrates, amino acids, fats, and fatty acids, and that they vary depending on the fermentation stage [81]. Tian et al. [82] detected DEGs in flavor compound pathways when the strains were used together and individually in the transcriptomic analysis of yogurts produced with *S. thermophilus* SIT-20.S and *L. delbrueckii* ssp. *bulgaricus* SIT-17.B strains. Furthermore, it has been reported that the use of *S. thermophilus* SIT-20.S increases acetoin accumulation due to the reduction in the gene encoding acetoin reductase (SIT-20S_orf01454). In the *S. thermophilus* SIT-20.S strain, the gene encoding acetaldehyde dehydrogenase (SIT-20S_orf00949) was upregulated, and it was reported that alcohol dehydrogenase expression was downregulated in both strains, thus maintaining acetaldehyde levels. On the other hand, it was emphasized that in the *L. delbrueckii* ssp. *bulgaricus* SIT-17.B strain, the gene encoding ADH oxidase (SIT-17B_orf00860) was upregulated, increasing the accumulation of acetoin and diacetyl.

Lipidomics is an omics approach that studies change in lipids in biological systems and characterizes the lipid profile [83]. Lipid types and structures (saturation, chain length, etc.) in foods, such as fatty acids, phospholipids, and sphingomyelins, can be easily identified using various chromatographic techniques such as Matrix-Assisted Laser Desorption Ionization (MALDI) MS, GC-MS, and LC-MS [84]. Advances in lipidomics applications allow for the efficient, accurate, and precise detailing of the roles of lipids in metabolic processes. Lipidomic characterization of dairy products plays an important role in applications such as quality control, composition analysis, and source identification [85]. Omics approaches and data analyses applied to various fermented dairy products are presented in Table 1.

Table 1. Omics approaches and data analyses applied to fermented dairy products.

Dairy Product	Target Compound/Microorganism	Omics Technology	Data Analysis	References
Fermented Yak Milk	Fatty acids Carbohydrates Volatile/aroma-related compounds Organic acids Microbial feature	Metagenomic Metabolomic	NMDS PLS-DA SHAP Spearman-Cytoscape	Meng et al. [86]
Sardinian Fermented Dairy Product (Gioddu)	Phosphatidylethanolamines Sphingolipids Glycerophospholipids Fatty acids Simple sugars Carboxylic acids Amino acids	Lipidomic Metabolomic	PCA PLS-DA OPLS-DA QC-SVRC	Manis et al. [87]
Fermented Goat Milk	Microbial community Organic acids Amino acid and derivatives Phospholipids Carbohydrates Glycosides	Metagenomic Metabolomic	Wilcoxon Rank-sum Kruskal–Wallis PCoA Random Forest STAMP Spearman Correlation PCA OPLS-DA	Wang et al. [88]
Fermented Milk	Volatile/aroma-related compounds Non-Volatile/aroma-related compounds Gene expression	Transcriptomic Metabolomic	PCA Volcano diagram Pathway enrichment rectangular tree	Cheng et al. [89]
Fermented Goat Milk	Differentially expressed metabolites Proteins Peptides	Metabolomic Proteomic Peptidomic	KEGG pathway PCA PCoA PLS-DA	Ge et al. [90]
Malty-Aroma Yogurt	Fermentation Metabolites (carboxylic acids and derivatives, benzene, organooxygen compounds, glycerophospholipids) Volatile/aroma-related compounds	Metabolomic Flavoromic	PLS-DA OPLS-DA PCA Spearman Correlation KEGG	Liu et al. [91]
Fermented Brown Goat Milk	Sensory-associated metabolites	Metabolomic Lipidomic	PCA OPLS-DA	Jia et al. [92]
Monascus Fermented Cheese	Microbial feature Volatile/aroma-related compounds	Metagenomic Flavoromic	PLS-DA KEGG COG functional annotation CAZy annotated	Wang et al. [93]

NMDS: non-metric multidimensional scaling; PLS-DA: Partial least squares discriminant analysis; SHAP: Shapley Additive exPlanations; PCA: Principal Component Analysis; OPLS-DA: Orthogonal Partial Least Squares-Discriminant Analysis; QC-SVRC: Quality Control Samples and Vector Regression Support; PCoA: Principal coordinates analysis; STAMP: Statistical Analysis of Metagenomic Profiles; COG: Clusters of Orthologous Groups; CAZy: Carbohydrate Active Enzymes.

However, while single-omics applications focus only on identifying a specific biological process, they are insufficient for characterizing the complex mechanisms behind microbial activity or interactions between components that occur during fermentation. Therefore, single-omics applications provide only a single result for the levels of components such as proteins, metabolites, or nucleic acids, and are even insufficient in fully representing metabolomes and proteomes under different transcriptional conditions [94]. In conclusion, the single-omics technologies described above provide important and valuable information within themselves. On the other hand, for an interactive and complex process like fermentation, in addition to more efficient and precise identification of key factors, the integration of multi-omics approaches is necessary to characterize both biochemical and microbiological mechanisms in a connected manner. Therefore, in this complex system, multi-omics applications have become an indispensable part of characterizing target molecules and all interactions with both an in-depth and holistic approach [25]. For

multiple applications, for example, integrating transcriptomic and metabolomic practices can aid in the discovery of metabolite–gene relationships by identifying regulatory genes and metabolic pathways involved in the production of specific metabolites. The integration of metabolomics and proteomics, enabling the identification of enzyme-assisted reactions affecting metabolite diversity and providing insights into post-translational modifications where metabolomics alone would be insufficient, can be presented as another example of a multi-omics approach [95]. Yuan et al. [96] used multi-omics approaches with metagenomic (deep sequencing), metabolomic (untargeted metabolomics) and proteomic (antibody chip protein detection) layers to elucidate the mechanism of antihypertensive activity of milk fermented with *L. plantarum* SR37-3 in hypertensive rats. The study concluded that administering fermented milk to rats significantly lowered their blood pressure, and this result was associated with partial inactivation of the renin–angiotensin system. Fermented milk has been reported to regulate key host metabolic pathways through the restructuring it induces in the gut microbiota, and this microbiota restructuring is linked to antihypertensive activity. Cheng et al. [97] investigated the physicochemical dynamics and metabolic process in fermented milk produced with the *L. delbrueckii* subsp. *bulgaricus* BG strain by integrating metabolomic and transcriptomic analyses. Multi-omics integration revealed that the primary energy pathway is glycolysis, and that fermentation, by restricting the TCA cycle, redirects pyruvate to lactate via lactate dehydrogenase (LDH and *ldhA*). It has been reported that upregulated peptidase genes contribute to the formation of hydrophobic dipeptides that cause bitterness, while genes for enhanced medium-chain fatty acid synthesis contribute to the formation of aroma compounds such as octanoic acid and n-decanoic acid.

Table 2 provides a summary comparing the advantages, limitations, and disadvantages of omics technologies, highlighting their suitability in terms of strengths and weaknesses. Therefore, this information will also contribute to a critical evaluation of the complementary roles of omics technologies in milk fermentation.

Table 2. Advantages, and limitations/disadvantages of omic technologies. [65,98–100].

Omics	Advantages	Limitations/Disadvantages
Metabolomic	- Assessment of gene function - Identifying bottlenecks in metabolic pathways - Identification of diagnostic biomarkers. - Providing phenotypic information	- High equipment cost - Chemical diversity of metabolomes - The fact that metabolites have short half-lives - Low amounts of metabolites and difficulty in analysis - Difficulties in sample preparation - Difficulties in determining the source of production and consumption of various metabolites in microbial communities - The limited number of metabolites identified - Limited availability of comprehensive reference databases and bioinformatics tools
Genomic	- Evaluation of genome modification - Low exposure to amplification distortions - High-throughput sequencing standardization - Recovery of the entire genome	- The inability to provide a complete definition on its own in complex biological systems - High computational requirements - Risk of contamination in low biomass samples - Host DNA susceptibility to contamination

Table 2. Cont.

Omics	Advantages	Limitations/Disadvantages
Proteomic	- Assessment of gene function - Evaluation of protein synthesis - Evaluation of post-translational modification - Identification of diagnostic biomarkers - Providing phenotypic information	- Difficulties in protein/peptide quantification - Errors in the analysis of unstable post-translational modification - High cost due to the use of advanced equipment - Difficulties in analysis due to low protein content. - Risk of cross-contamination during enzymatic proteolysis - Difficulties in the expression of the entire proteome due to the large number of proteins - Challenges in standardization, repeatability, and reproducibility in sample preparation - Difficulties in finding optimized protein sequence databases
Transcriptomic	- Assessment of gene function through mRNA transcripts - The possibility of 16S rRNA sequencing to reconstruct phylogenies - Analysis of the expression profiles of the identified genes - Determining the functional characteristics of the microbial community	- Inability to identify phenotypes on its own - Insufficient information due to post-translational modification - Risks of cross-contamination and cross-hybridization - Complexity of the data - Lack of sufficient information regarding cell viability or the expression profiles of identified genes - Challenges in preparing an unbiased and high-quality RNA sample - Risk of host RNA contamination
Multi-omics	- Determination of diagnostic biomarkers with high accuracy - Providing comprehensive information about biological systems	- High data size and data complexity - High cost - Creating an experimental design encompassing single and multi-omics approaches and all parameters - Challenges in using advanced analytical methods - Requires expertise for using advanced data integration approaches

Multi-omics approaches help improve accuracy and precision in small-scale data by filling in unreliable or incomplete information. Therefore, techniques such as cross-validation analysis or targeted correlation allow for the accurate characterization of many biomarkers, including key genes, dominant strains, important proteins, enzymes, or characteristic aroma components [94,101]. The quality of fermented products primarily depends on the functional interactions within their microbial population. On the other hand, the fact that traditional fermentation proceeds through a spontaneously developing microbial process highlights its sensitivity to parameters such as raw material composition, variables in operational practices, and environmental factors. Therefore, the variability that naturally occurs in the production process creates challenges in achieving standardization and quality products [102]. In this context, the characterization of fermented products using multi-omics technologies has gained significant momentum in recent years. Thanks to this technological advancement, microbial composition, DEGs, metabolic pathways, and protein expression levels can be examined in more detail during the fermentation process. Although fermented foods exhibit metabolic differences depending on microorganisms, substrate, environment, and processing conditions, proteins, amino acids and their derivatives, carbohydrates, fatty acids, polyphenols, organic acids, nucleotides, vitamins, and flavonoid compounds essentially comprise fermentation metabolites [103]. By integrating various omics applications to characterize the fermentation process, comprehensive databases can be created, providing significant support for further research and applications. Thanks to the databases created, multidimensional data can be systematically compiled, and fundamental information about fermentation components

or microorganisms can be easily discovered. For example, curatedFoodMetagenomicData (cFMD), which integrates more than 2500 food-derived metagenomic datasets; Omics Data Resource from Microorganisms Associated with Fermented Foods (ODFM), a specialized database containing 131 bacterial, 28 eukaryotic, and 38 archaeal genome sequences associated with fermented foods; and the FoodMicroDB database, containing 6358 sequence entries and 4710 microorganism taxonomies classified with EasyAmplicon, stand out in this field. In addition, for the purpose of examining optimized fermentation processes, the FermFoodDb database offers 2205 entries covering key fields such as peptide sequence, food source, mass and IC50, functional activity, starter culture, fermentation conditions, in vitro or in vivo test conditions for the sequences, analysis method, and model type. Additionally, there is the Fermented Dairy Food Database (FDF-DB), a database containing process details and taxonomic information for 1852 traditional dairy products such as yogurt, cheese, and fermented milk, compiled from collected metadata [64,103,104].

In omics approaches, such as those used to assess gene and protein expression, genetic variants, or epigenetic modifications, batch effects arising from differences in reagents, laboratory conditions, or personnel should not be overlooked. Errors here can result in mistakes indicating a relationship between biological and technical variables. Controlling all aspects from start to finish, such as reagents, personnel, laboratory conditions, and storage, can minimize errors [105]. Furthermore, in omics approaches, other factors such as background noise heterogeneity, effect size, sample size, and information flow also contribute to these errors [106]. Accordingly, it can be concluded that omics datasets are highly sensitive to processing applied at every step, such as sample collection and preparation protocols, analytical procedures, laboratory conditions, technical changes, etc. Ultimately, biological variability and these parameters, which are often overlooked in data collection, can limit the clarification of true relationships, reproducibility, and accuracy. In multi-omics approaches, experimental protocols, the collection of standardized metadata, and validated reference materials are crucial steps for comparing data. Here, the FAIR (Frequently Available, Accessible, Interoperable, and Reusable) principle comes to the forefront, offering solutions to problems by improving stages such as data collection principles, the use of publicly available data repositories, collaborative model development, and repeatability [106,107].

4. Multi-Omics Data Integration Strategies

The integration of multi-omics data provides information about biomolecules from different layers and holds promise for a systematic and holistic understanding of complex processes such as fermentation. Integrated approaches for exploring intermolecular interactions combine individual omics data sequentially and simultaneously. Therefore, they assist in the flow and evaluation of information from one omics level to another [108,109]. On the other hand, these multi-factor and multi-layered approaches make the work quite difficult from a computational point of view, and are even challenging to present and understand visually. When developing methods or approaches for integrating omics data, it is important not to overlook the fact that each data type has a complex structure and requires a different level of completeness. For example, the interpretation of genome and transcriptome data in relation to biological function represents the biggest limitation for these omics. This limitation can be overcome by combining metabolomic and proteomic data with genomic and transcriptomic data to provide molecular insights by correlating epigenetic and genetic variation with phenotypic variation [110]. In multi-omics data integration, various strategies such as message forwarding, component-based methods, Bayesian methods, classification schemes, and network analysis have been proposed as solutions to answer various questions. Data-driven methods include techniques such as Bayesian Consensus Clustering and Similarity Network Fusion, while methods for characterizing common variations include

Joint Non-negative Matrix Factorization, sparse MultiBlock Partial Least Squares, Joint and Individual Variation Explained, sparse Generalized Canonical Correlation Analysis (sGCCA), and Multi-Omics Factor Analysis (MOFA) [111]. In multi-omics data integration approaches, the merging of different omics layers can be classified in relation to stages: early fusion (feature merging), intermediate fusion (estimating common representations), and late fusion (merging sample relationships or graphs). Early fusion is essentially defined as data-level integration and involves combining multi-omics datasets into a single feature matrix before ML or statistical analysis. Therefore, early fusion allows thousands of molecular variables to be evaluated simultaneously, providing a comprehensive description of biological systems. On the other hand, early fusion has some disadvantages, such as high dimensionality and overfitting issues. For example, when studying fermentation dynamics, variables such as feature numbers and biological resolution differ across metabolomic, transcriptomic, microbiome, and proteomic datasets, and therefore direct merging can lead to overrepresentation of high-dimensional datasets and computational complexity. Intermediate fusion, described as feature or representation-level integration, integrates omics datasets after transforming each data layer into similarity networks or latent variables. Therefore, it preserves the structure for the layer and establishes integration between omics approaches. Methods such as SNF, RGCCA, DIABLO, and MOFA are representational intermediate fusion approaches because they integrate transformed representations instead of raw features. Intermediate fusion effectively determines the interactions between omics layers, but it can also mask some biological signals during the transformation process. In the latest fusion based on ML methods, instead of integrating raw or transformed datasets, it combines the outputs of models trained separately on each omics layer. Here, each omics layer is modeled independently, and predictions are made using strategies such as weighted averages, clustering algorithms, and majority voting [112–116].

When MOFA is provided with a matrix that involves the evaluation of multi-omics data types on the same or partially overlapping sample sets, it can offer an interpretable low-dimensional data representation in terms of latent factors. Thanks to the learned factors, it captures the main source of variations between data types, making it possible to determine continuous molecular gradients or separated subgroups of samples, detect outliers, and complete data [117]. On the other hand, Similarity Network Fusion (SNF) solves data complexity by creating sample networks for each data type and efficiently and effectively combining them in a single network in a nonlinear manner to represent the entire spectrum of the underlying data. Here, the combined network captures information from different data sources that are shared and complementary, and each data type provides insight into the similarities between samples. Since SNF is a method based on sample networks, it allows for the acquisition of useful information even with a small number of samples, while also being highly resistant to heterogeneity and noise. In addition to integrating data with SNF, combined networks can be clustered to effectively identify subtypes among existing samples, and the resulting network can then be used to predict labels for new samples [118]. Metabolomic studies often involve measurements from different omics approaches that can contain hidden biological information, and independently evaluating each biological domain can hinder the revelation of this information. To overcome this obstacle, multi-block methods such as Regularised Generalised Canonical Correlation Analysis (RGCCA) and Data Integration Analysis for Biomarker Discovery Using Latent Components (DIABLO) are preferred for examining relationships between data measured with different approaches and identifying subsets of variables [119].

Becchi et al. [95] reported that techniques such as Multiple Co-inertia Analysis (MCIA) and DIABLO were used to determine biomarkers in cheese fermentation. MCIA is an unsupervised method for identifying correlations between high-dimensional datasets, reflecting

these correlations on a common denominator to facilitate biological interpretability and pathway analysis. DIABLO is a supervised approach that integrates multiple datasets, reveals relationships with a categorical outcome variable, and maximizes covariances across all dataset pairs. Therefore, it is possible to identify a multi-omics signature that better distinguishes the target outputs [95,119]. Afshari et al. [120] reported that the biomarkers, including taxa and metabolites, of cheddar cheeses produced from the same manufacturer and with the same properties can be successfully identified and sequenced at the molecular level with the application of multi-omics and data integration (DIABLO). Ultimately, these methods help in more comprehensive evaluation and the discovery of more accurate and biologically relevant biomarkers by utilizing aggregated information from different omics layers in a complex process such as fermentation control. On the other hand, based on this information, although ML and DL models offer high predictive performance in integrating multi-omics data, their biological interpretability poses a significant challenge. Therefore, in recent years, Explainable Artificial Intelligence approaches have come to the forefront in order to overcome these challenges.

While the integration of multi-omics data under controlled laboratory conditions offers significant potential, its application in industrial milk fermentation presents several challenges. In the laboratory, experimental designs are generally carried out with standard raw materials, limited samples, controlled conditions, and relatively more stable microbial communities compared to industry. On the other hand, in industrial-scale production with multi-omics data integration, in addition to the differences in all these parameters, challenges arise such as the computational requirements in data preprocessing, normalization, storage, and model training due to the formation of large-scale heterogeneous datasets. Ultimately, these challenges make it difficult to implement reliable, standardized, and easily applicable multi-omics data integration in milk fermentation at the industry level, and bring to the forefront the need for standardized workflows and scalable computational infrastructures. The workflow for multi-omics data and artificial intelligence data integration approaches in dairy fermentation is presented in Figure 4.

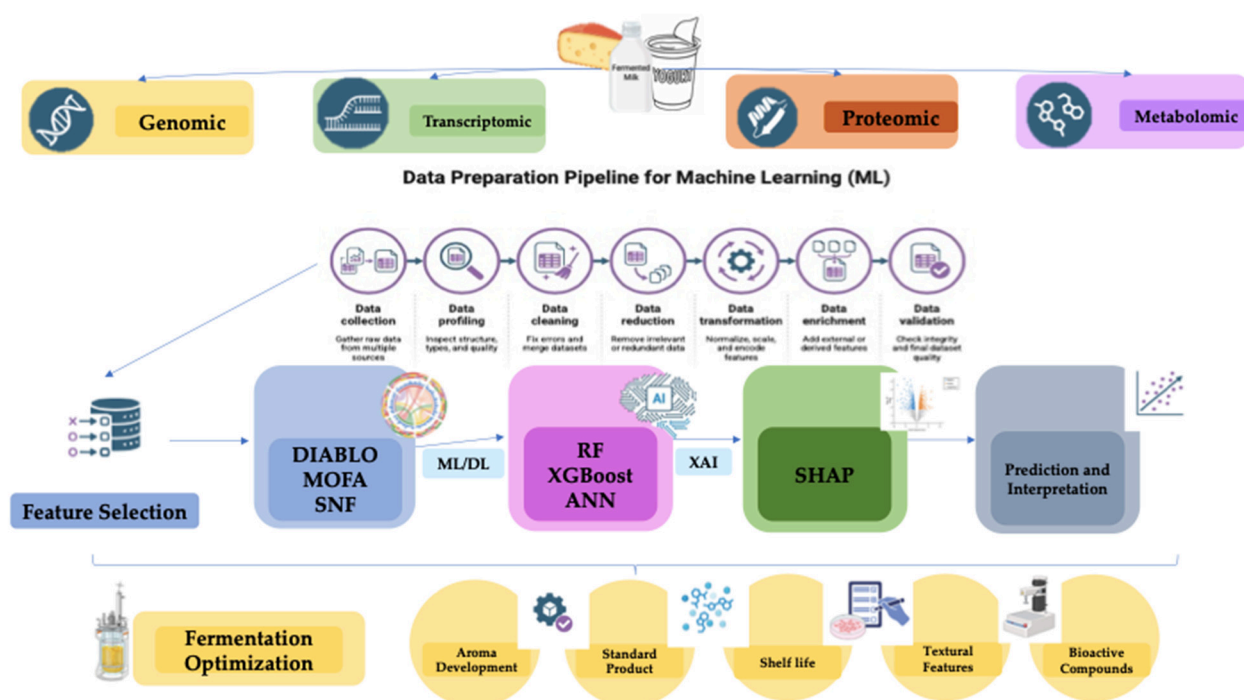


Figure 4. Workflow for multi-omics data and artificial intelligence data integration approaches in dairy product fermentation (<https://www.biorender.com> (accessed on 20 June 2026)).

5. Artificial Intelligence-Based Modeling of Dairy Fermentation

Although omics methods present various technological challenges, such as required sample size, sample preparation, instrumentation sensitivity, sequencing depth requirements, and molecular dynamic range, they provide complete information on a single regulatory layer. On the other hand, the combined use of omics technologies in understanding biological processes based on highly complex molecular mechanisms—that is, a multi-omics approach that considers the molecular layers constituting the system in a holistic manner—offers a solution [121,122]. The high dimensionality of data obtained with omics technologies and significant variations between modalities pose a disadvantage for early multimodal data fusion involving traditional statistical techniques. This phenomenon, often described as the “curse of dimensionality”, refers to the difficulty in clarifying the relationships between variables as the number of variables per data point increases. In summary, as the number of dimensions, or variables, increases, processing and analyzing the dataset becomes more difficult, and the computational requirements increase. Additionally, while high-dimensional data tend to be too sparse to fit meaningful distributions, they are equally likely to fit spurious relationships or noise, which is another problem. Data obtained through omics technologies are also highly susceptible to variability and noise due to factors such as biological variations and measurement errors. In this context, researchers have recently been using artificial intelligence algorithms to overcome the dimensionality problem in the analysis of high-dimensional data [123,124]. Artificial intelligence, used in controlling and optimizing the production chain and improving product quality, is described as a science that mimics and surpasses human intelligence [125]. Statistical analysis methods used in the analysis of data obtained from omics applications include various bioinformatics and artificial intelligence-based approaches such as machine learning (ML), deep learning, and multi-omics data integration. Statistical analysis methods such as correlation analysis (Person and Spearman correlation), differential expression analysis, regression analyses (Chi-square, multinomial regression, logistic regression, and generalized linear model), and network analysis can be exemplified as computational methods used in the analysis and integration of multi-omics data [101]. Linear regression is preferred for modeling the linear relationship between feature variables and continuous response variables. In fermentation, modeling the relationship between parameters such as temperature, time, and humidity, and product indicators, offers advantages in terms of computational efficiency and strong interpretability [126].

ML, which can evaluate complex data in scenarios where traditional statistical methods are insufficient, is defined as a data analysis technique that trains computational models to learn information from data, define boundaries, and make decisions. In dynamic processes where many variables and metabolic pathways, such as fermentation, are effective, ML feature selection, pattern discovery, and biomarker identification are preferred, as well as prediction and classification modeling across various omics layers [127]. ML techniques are classified into two categories: Unsupervised ML, which extracts patterns from data without predefined information about dependent class labels, and Supervised ML, where information referred to as a training set is predefined and then classification is performed to predict new outcomes [128]. Unsupervised ML helps group similar variables into different categories and reveal potential structures or patterns within the data [46]. In multi-omics data integration, hierarchical clustering (HC) and k-means clustering are preferred for unsupervised ML methods, while for supervised ML, various artificial intelligence-based approaches such as Random Forest, Support Vector Machine (SVM), Decision Tree, XGBoost, k-Nearest Neighbor (kNN), and Artificial Neural Network (ANN) are preferred [101,128]. Furthermore, in Multivariate Analysis (MVA), Orthogonal Partial Least Squares–Discriminant Analysis (OPLS-DA), Partial Least Squares–Discriminant Analysis (PLS-DA), and PLSR are catego-

alized as supervised MVA and MANOVA, while Principal Component Analysis (PCA) and Principal Coordinates Analysis (PCoA) are categorized as unsupervised MVA [101]. PCA, a classic unsupervised dimensionality reduction model, is a preferred statistical method for demonstrating dominant variation patterns in data. By reducing complex multi-omics data to a few key components, it provides intuitive observations about structure and trends [129]. PLS models, which are controlled dimensionality reduction methods, include category information and enable the selection of the most important feature variables in classification. PLS models are preferred for modeling parameters such as estimating microbial metabolic activities, differentiating microorganism types, and determining the flavor profile and sensory quality of fermented products [126]. It is stated that the fermentation stages are reliably evaluated using Random Forest, SVM and Multilayer Perceptron (MLP) prediction models and HCA clustering results in estimating the degree of fermentation [125].

Deep learning (DL) is a branch of ML and has gained considerable popularity due to its ability to identify complex and nonlinear patterns in data. It offers a robust generalization capability within an efficient framework for processing high-dimensional multi-omics data, enabling accurate prediction of invisible data [130]. DL is a paradigm consisting of multilayered neural networks that extract progressively higher-level abstractions from raw experimental data and transform them into biologically meaningful outputs [131]. Unlike traditional methods that consider microbial dynamics and spatial organization as independent variables in fermentation, DL reveals how microbial activities shape the fermentation dynamics. Therefore, it contributes to the optimization of fermentation conditions by enabling the early and rapid detection of metabolic or microbial abnormalities that may occur during fermentation [132]. Indeed, Rugji et al. [133] reported that artificial intelligence algorithms contribute to the optimization of the quality and yield of the final product, as well as the cost-effective management of the process, by adjusting norms such as pH, temperature, and time through the analysis of data obtained from fermentation tanks. In fermented dairy products, the quality of the final product is primarily influenced by the growth kinetics of the starter cultures and the interaction between the microbial community. It has been confirmed by Saetae [134] that artificial intelligence-based models can optimize the fermentation process by predicting acidification and microbial growth. Here, Long Short-Term Memory (LSTM) neural networks were used for microbial prediction and Support Vector Regression (SVR) for pH acidification dynamics. The hybrid LSTM model was found to be superior at 37 °C and 41 °C in capturing temperature-dependent growth patterns in specific strains, while SVR performed well for acidification prediction. The research results reported the potential of hybrid ML methods for real-time fermentation monitoring, standardized product manufacturing, and intelligent control management in production. However, aroma and flavor development are crucial for consumer acceptance and quality of fermented dairy products. The combined use of omics applications such as metabolomics and volatilomics, and their integration with ML, has made it possible to obtain detailed information about aroma formation mechanisms. A recent study revealed the metabolic pathways involved in the formation of dynamic aroma phenotypes during yogurt fermentation using metabolomic, volatilomics, and sensomics approaches [27]. Ultimately, such studies provide valuable data for artificial intelligence-based prediction of fermentation and aroma relationships and for optimizing the process. However, cheese quality is associated with dynamic complex interactions between metabolites, cheese microbiota, and milk substrates. Becchi et al. [135] investigated the effects of ripening, altitude region, and rind ratio parameters on the quality of Parmigiano Reggiano hard cheese using a targeted metabolomics approach combined with ML chemometrics. It has been reported that amino acids and lipids are distinctive metabolites during the ripening period and that the random forest model reaches acceptable accuracy levels in shell ratio estimation. Yang et al. [136]

reported that when ML is combined with sensory verification, it contributes to understanding the contribution of *S. thermophilus* to the aroma profile in fermented milk production and provides information on the precise regulation of flavor in these products. Multi-omics applications and ML integration in probiotic research consist of 5 main modules: (1) Study design, (2) Layer-specific preprocessing, (3) Feature representation, (4) Cross-omics integration, and (5) Model interpretation through experimental feedback. Therefore, this module answers the questions of how to sort data within the framework of different spatial and temporal scales, how to express complex molecular features in a holistic analytical field, and by what stage/mechanism to integrate information from multiple sources [137].

No single ML algorithm consistently outperforms others in all milk fermentation applications. Model selection should depend on the dataset size, data type (e.g., spectral, image, or multi-omics), forecasting objectives, and computational resources. Tree-based algorithms are generally advantageous for small to medium-sized datasets with high interpretability, whereas DL approaches typically achieve superior performance when dealing with large and complex datasets. Therefore, algorithm selection should be guided not only by prediction accuracy but also by the biological question and data characteristics. Table 3 summarizes the main strengths and weaknesses of the most commonly used artificial intelligence algorithms in milk fermentation and related food applications. Algorithm selection should be guided by data characteristics, prediction goals, and computational constraints, rather than by the selection of a universally superior model.

Table 3. Strengths and weaknesses of the most commonly used artificial intelligence algorithms in food applications [100,138–142].

Artificial Intelligence Approach	Strengths	Limitations
Random Forest	- It is capable of processing unbalanced datasets. - It is effective in reducing excessive conformity tendencies.	- It is difficult to interpret how the decisions were made. - There may be situations requiring careful hyperparameter adjustment. - It generally performs well on small to medium-sized datasets.
SVM	- It is effective in identifying nonlinear and complex data. - It is effective in processing high-dimensional datasets.	- It requires a longer training time compared to other algorithms. - Because it is sensitive to hyperparameter selection, its performance can be affected.
KNN	- It is simple and easy to implement. - It is effective in identifying nonlinear patterns.	It is highly sensitive to outliers and noise.
ANN	- It can learn patterns in complex and nonlinear data. - It is effective in processing both structured and unstructured data.	- It requires large datasets for standard generalization. - Model complexity and training time are important parameters in determining performance.
XGBoost	- It stands out for its accuracy and high performance. - It is able to efficiently process unbalanced datasets.	- Careful hyperparameter adjustment may be required. - Training duration and model complexity are important parameters.
Logistic regression	- It stands out with its simple application and ease of interpretation. - It can identify linear patterns in data. - It is useful in situations where things are simpler and more straightforward.	It is not effective in detecting anomalies in complex and unbalanced datasets.

Table 3. Cont.

Artificial Intelligence Approach	Strengths	Limitations
LSTM	• It stands out in the areas of temporal learning, robust nonlinear modeling, and selective discrimination.	• More memory and training time are required. • It requires consecutive time series data.
Multi-scale feature fusion, CNN + FNN	• It stands out in terms of high prediction accuracy, reliability, and robust nonlinear feature learning.	• It is data-hungry and has high processing power requirements. • The complex structure presents challenges in evaluation. • It has high calculation costs.

6. Explainable Artificial Intelligence (XAI) for Dairy Fermentation

Artificial intelligence methods have significant potential in monitoring and predicting the fermentation process. Integrating artificial intelligence methods with multi-omics datasets enables the acquisition of more comprehensive molecular insights and the development of more reliable and applicable models for optimizing fermentation. Although ML and DL approaches stand out in controlling the fermentation process with their high prediction performance, beyond prediction accuracy, interpreting complex models and understanding mechanisms in biological systems remain challenges and limitations [143,144]. In this context, explainable artificial intelligence (XAI) approaches have emerged to clarify the contribution of variables and increase the transparency of artificial intelligence-powered decision-making processes [145,146]. XAI methods provide insights into how AI models generate predictions by identifying the contribution and significance of input variables. Furthermore, these approaches facilitate the interpretation of the complex relationships between microbial communities, environmental parameters, metabolites, and final product characteristics during the fermentation process. Therefore, integrating XAI with multi-omics datasets offers promising strategies that move beyond fermentation prediction to mechanistic understanding. Ultimately, XAI-based approaches can contribute to the identification of critical molecular characteristics, microorganism selection, biomarker discovery, and fermentation optimization using data obtained during the fermentation process [147,148].

When AI outputs are used to support quality and reliability-related decisions in commercial fermentation processes, it is particularly important to pay attention to interpretability, because it is necessary to understand the variables that drive model predictions before operators can implement process interventions. Beyond SHapley Additive exPlanations (SHAP), other XAI approaches can offer a complementary perspective in interpreting complex fermentation dynamics. Here, Local Interpretable Model-Agnostic Explanations (LIME) works by distorting the input data around a particular observation and fitting a simple and interpretable model for a local approximation of the behavior of the original black box model [149]. Although its interpretation is local in nature, LIME can actually be useful in fermentation prediction by identifying molecular and biological process variables. In DL models, attention mechanisms offer another approach by selecting learned weights based on the input characteristics or representations and their contribution to the model’s prediction process. In interpreting multi-omics data, attentional mechanisms can be preferred for focusing on biologically significant modules in heterogeneous omics datasets [150]. On the other hand, it is important that attention weights should not be interpreted as precise measures of feature importance, and that biological interpretations are supported by complementary XAI approaches and experimental evidence [151]. These approaches essentially offer complementary strategies for interpreting complex artificial

intelligence models. SHAP emphasizes feature attribution analysis, LIME focuses on local model behavior, and attention mechanisms highlight representations of information learned in deep neural networks.

Digital twin (DT), a complementary tool for simulating fermentation systems, represents a virtual copy of a physical bioprocess. DT simulates process dynamics and is continuously updated with real-time data for process optimization. During the fermentation process, microbial growth, gas transfer, metabolite flow, and product formation can be modeled using DT in response to various dynamic input variables such as pH, temperature, oxygen, and nutrient concentration. Furthermore, the model can be calibrated using historical data and validated with a real-time feedback loop. Moreover, when integrated with artificial intelligence, DT turns into prediction engines where “what if” scenarios can be tested without risking actual production [152]. Singh and Kumar [125] report that in a simulation created to control fermentation dynamics using genetic algorithms (GA), the DT-based strategy successfully adjusted variables such as dissolved oxygen and pH, thereby increasing microorganism growth and carbon source utilization and improving fermentation efficiency. Adeleke et al. [153] used integrated Internet of Things (IoT) and ML framework for precise fermentation control of the fermented milk product Amasi by collecting pH, temperature and electrical conductivity data on a Raspberry Pi-based platform and transmitting them to DT via RESTful APIs. Electrical conductivity data were calibrated according to titratable acidity using ML models, and Convolutional neural networks (CNN) achieved the highest prediction accuracy, followed by feedforward neural networks (FNN) and Random Forest. The researchers developed a model of time to reach target acidity, taking into account fermentation conditions and desired acidity levels. In another study by the same research team, an integrated DT platform was presented that combines IoT sensors and ML with closed-loop PID temperature and stirring control for the fermentation of Amasi. Here, four image-based strategies (CNN-based deep embeddings, local binary patterns (LBP) + Gabor texture, LAB (L, a and b values)) and four hybrid strategies were evaluated using fully connected neural network, XGBoost and Random Forest models. The researchers emphasized that the low-cost hardware and cloud-based DT approach can be applied to other fermented dairy products [154]. In cheese production, the effects of metabolic processes of *L. lactis*, *L. plantarum*, and *Propionibacterium freudenreichii* on sensory characteristics were investigated using genome-scale metabolic models and omics data integration, examining single-culture experiments and individual dynamics. With DT, the dynamics of the microbial community were accurately predicted, and the contribution of each microorganism species to sensory compound production was elucidated. As this research demonstrates, the importance of dynamic metabolic modeling in understanding the fermentation process is noteworthy [155]. Lundberg and Lee [156] stated that there is a tension between accuracy and interpretability when evaluating high modern datasets using models such as ensemble or DL. On the other hand, recent proposals for interpreting predictions of complex models have highlighted uncertainties regarding how these methods relate to each other and which method should be preferred. The researchers reported that these uncertainties can be resolved using SHAP, which assigns an importance value to a specific prediction of each feature, and that the predictions can be interpreted within a unified framework. SHAP consists of two components: the definition of a new class of additive feature importance measures, and theoretical results demonstrating that a unique solution with the desired properties exists within this defined class. Combining six methods, SHAP defines a class of additive feature importance methods and ultimately stands out as a unique solution that matches the desired properties within this class. Therefore, SHAP has gained importance in improving the accuracy and biological interpretability of complex ML and DL methods in the evaluation of multi-omics data. Yang et al. [136] trained and

evaluated multi-supervised ML models using quantitative data of 15 compounds from 24 strains of *S. thermophilus* used in fermented dairy products as determinants of aroma profile and sensory characteristics. To ensure a balance between predictive accuracy and interpretability in identifying the compounds underlying the creamy aroma, researchers applied six high-performance SHAP analyses: XGB, passive-aggressive, Linear SVC, SGD, LDA, and GB. SHAP analysis revealed that 2,3-butanedione, 2,3-pentanedione, and δ -decalactone were the most effective compounds contributing to the creamy aroma. The researchers reported that significant information regarding aroma formation in fermented dairy products was obtained using an ML-focused framework, and a reliable data-driven strategy was presented for targeted screening of aroma-based starter cultures. The workflow involving omics data and XAI approaches in dairy product fermentation control is given in Figure 5.

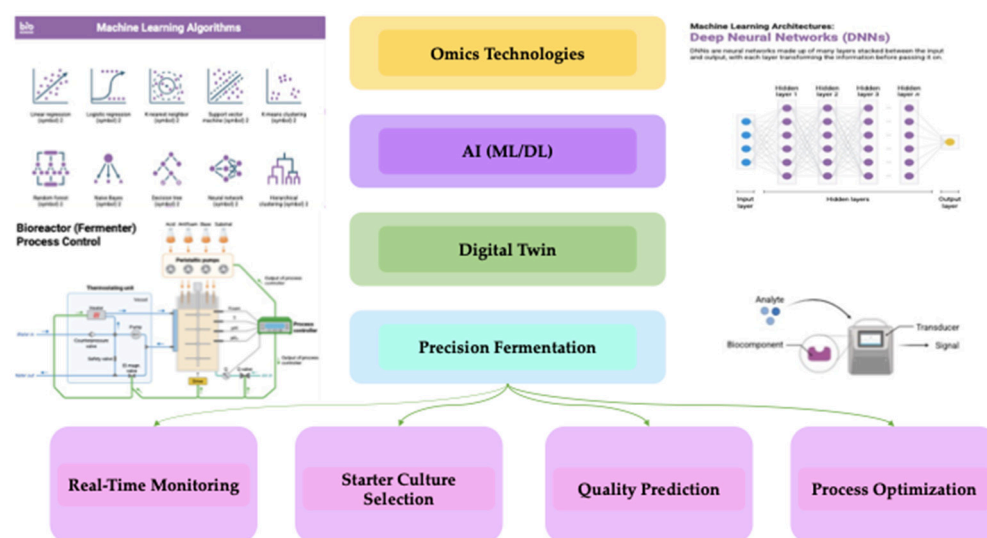


Figure 5. Workflow involving omics data and explainable artificial intelligence approaches in dairy product fermentation control (<https://www.biorender.com> (accessed on 20 June 2026)).

7. Conclusions and Future Perspectives

The fermentation of dairy products is a complex biological process shaped by the dynamic interaction of substrates, microbial communities, metabolites, and environmental factors. This review emphasizes that multi-omics approaches provide molecular-level information about fermentation by correlating processes such as gene expression, microbial composition, protein conversion, and metabolite production, thus facilitating a better understanding of the process. However, the integration of multi-omics datasets with advanced computational approaches such as ML, DL, and XAI represents a reliable step towards data-driven and predictive fermentation dynamics control. Although multi-omics technologies and artificial intelligence-based modeling approaches have provided important insights into understanding the process at the molecular level in dairy fermentation, several challenges remain in fully integrating these methods or technologies into routine scientific research or industrial production. Metabolomics, genomics, proteomics, or transcriptomics approaches differ significantly in terms of the structure, scale, and size of the data. Therefore, evaluating data from different omics layers together becomes difficult, and up-to-date computational methods are needed for data integration. Additionally, limitations in multi-omics approaches include missing data in terms of reproducibility, biological interpretability, and generalizability, small sample sizes, batch effect, and high computational costs. Ultimately, the importance of multi-omics data integration methods such as DIABLO, SNF, and MOFA in overcoming these limiting factors is noteworthy.

Through these methods, which have been discussed in detail earlier, the relationships between microbial communities, metabolite formation, hydrolysis in proteins or fats, and sensory quality characteristics can be evaluated and explained in a holistic approach. On the other hand, in addition to these methods, XAI approaches make a significant contribution to eliminating uncertainties in relationships that cannot be obtained from ML and DL models and that remain hidden. For example, SHAP can reveal the effects of genes, metabolites, and proteins on outputs, while DT can facilitate fermentation optimization. XAI approaches make it possible not only to make accurate predictions but also to explain biological mechanisms and eliminate uncertainties. Furthermore, DT, developed by combining multi-omics data, IoT and artificial intelligence-based models in dairy fermentation, contributes significantly to advancements in this field. This system, which simulates fermentation, offers advantages such as real-time monitoring, optimization of the production process, and early error detection. Ultimately, this allows for standardized, high-quality, and sustainable production, and the completion of fermentation with minimal losses. As a result, thanks to these technologies, the fermentation of dairy products is moving from a descriptive approach to a data-driven and predictive one. Furthermore, the fact that most current studies are based on laboratory-scale experiments and that validation under industrial fermentation conditions is limited remains a challenge. In the future, the widespread adoption of multi-omics data integration methods in both industrial and scientific studies, and the real-time implementation of these systems, indicates that precision fermentation applications can be used across a wider range. Ultimately, these approaches have the potential to transform dairy fermentation from an empirical process into a predictive and precise biotechnological platform.

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References

1. Yang, S.; Bai, M.; Kwok, L.Y.; Zhong, Z.; Sun, Z. The intricate symbiotic relationship between lactic acid bacterial starters in the milk fermentation ecosystem. *Crit. Rev. Food Sci. Nutr.* **2025**, *65*, 728–745. [[CrossRef](#)] [[PubMed](#)]
2. Obayomi, O.V.; Malomo, A.A.; Olaniran, A.F.; Osemwegie, O.O.; Olojede, A.O.; Beyioku, O.E.; Adeyemi, O.S. Transition from fermentation to precision fermentation: Role in sustainable food system. *Biotechnol. Rep.* **2026**, *50*, e00952. [[CrossRef](#)] [[PubMed](#)]
3. Sokra, I.; Somaly, S.; Kong Mey, R.L.; Marady, V. Factors influencing fermentation efficiency and product quality: A comprehensive review. *J. Agric. Technol.* **2026**, *2*, 109–117. [[CrossRef](#)]
4. Ağagündüz, D.; Ertaş Öztürk, Y.; Ayhan, B.; Bulmuş-Tüccar, T.; Özenir, Ç.; Erdoğan Gövez, N.; Ozogul, Y.; Esatbeyoglu, T.; Ozogul, F. Certain fermented dairy foods as a source of multibiotics and multimetabolites: A comprehensive review. *Front. Nutr.* **2025**, *12*, 1678150. [[CrossRef](#)] [[PubMed](#)]
5. AlSulaiti, B.; Ferguson-Smith, A.C.; Hanin, G. From mammary glands to nutrients: Genetic insights into milk composition. *Biol. Reprod.* **2026**, *114*, 442–461. [[CrossRef](#)] [[PubMed](#)]
6. Gemechu, T. Review on lactic acid bacteria function in milk fermentation and preservation. *Afr. J. Food Sci.* **2015**, *9*, 170–175. [[CrossRef](#)]

7. Ren, Q.; Zhang, J.; Chen, X.; Pang, J.; Wichers, H.J.; Wen, Y.; Hettinga, K.A. Effects of fermentation on protein digestion and peptide release in an in vitro adult digestion model. *Food Res. Int.* **2026**, *230*, 118670. [[CrossRef](#)] [[PubMed](#)]
8. Shahein, M.R.; Elkot, W.F.; Albezrah, N.K.A.; Abdel-Hafez, L.J.M.; Alharbi, M.A.; Massoud, D.; Elmahallawy, E.K. Insights into the microbiological and physicochemical properties of bio-frozen yoghurt made with probiotic strains in combination with Jerusalem artichoke tubers powder. *Fermentation* **2022**, *8*, 390. [[CrossRef](#)]
9. Wu, T.; Guo, S.; Liu, K.; Kwok, L.Y.; Wang, J.; Zhang, H. Exploring the postbiotic potential of multi-strain pasteurized fermented milk: A metabolomics study. *LWT* **2024**, *209*, 116802. [[CrossRef](#)]
10. Antsyperova, M.; Arseneva, T.; Fedorov, A.; Lemeshonok, E.; Zabodalova, L.; Baranenko, D. Probiotics selection for low-lactose fermented goat milk products. *Sustain. Food Technol.* **2026**, *4*, 1596–1614. [[CrossRef](#)]
11. Hill, D.; Sugrue, I.; Arendt, E.; Hill, C.; Stanton, C.; Ross, R.P. Recent advances in microbial fermentation for dairy and health. *F1000Research* **2017**, *6*, 751. [[CrossRef](#)] [[PubMed](#)]
12. Iskandar, C.F.; Cailliez-Grimal, C.; Borges, F.; Revol-Junelles, A.M. Review of lactose and galactose metabolism in lactic acid bacteria dedicated to expert genomic annotation. *Trends Food Sci. Technol.* **2019**, *88*, 121–132. [[CrossRef](#)]
13. Ağagündüz, D.; Yılmaz, B.; Şahin, T.Ö.; Güneşliol, B.E.; Ayten, Ş.; Russo, P.; Spano, G.; Rocha, J.M.; Bartkiene, E.; Özogul, F. Dairy lactic acid bacteria and their potential function in dietetics: The food–gut–health axis. *Foods* **2021**, *10*, 3099. [[CrossRef](#)] [[PubMed](#)]
14. Ibrahim, S.A.; Yeboah, P.J.; Ayivi, R.D.; Eddin, A.S.; Wijemanna, N.D.; Paidari, S.; Bakhshayesh, R.V. A review and comparative perspective on health benefits of probiotic and fermented foods. *Int. J. Food Sci. Technol.* **2023**, *58*, 4948–4964. [[CrossRef](#)]
15. Nami, Y.; Barghi, A.; Sadeghi, M.; Farhadi, T.; Haghshenas, B. *Lactobacillus delbrueckii*: A functional powerhouse in dairy fermentation and emerging probiotic applications. *Food Sci. Nutr.* **2026**, *14*, e71546. [[CrossRef](#)] [[PubMed](#)]
16. Bintsis, T.; Papademas, P. The evolution of fermented milks, from artisanal to industrial products: A critical review. *Fermentation* **2022**, *8*, 679. [[CrossRef](#)]
17. Bintsis, T. Lactic acid bacteria as starter cultures: An update in their metabolism and genetics. *AIMS Microbiol.* **2018**, *4*, 665. [[CrossRef](#)] [[PubMed](#)]
18. Kouakou-Kouamé, A.C.; N’guessan, F.K.; Montet, D.; Djè, M.K. Production of flavor compounds by lactic acid bacteria in fermented foods. In *Lactic Acid Bacteria as Cell Factories*; Montet, D., Ray, R.C., Azevedo, V.A.D.C., Paramithiotis, S., Eds.; Woodhead Publishing: Cambridge, UK, 2023; pp. 239–270. [[CrossRef](#)]
19. Ghailan, A.Z.; Niamah, A.K. *Streptococcus thermophilus*: Metabolic properties, functional features, and useful applications. *Appl. Microbiol.* **2025**, *5*, 101. [[CrossRef](#)]
20. Shibby, V.K.; Mishra, H.N. Fermented milks and milk products as functional foods—A review. *Crit. Rev. Food Sci. Nutr.* **2013**, *53*, 482–496. [[CrossRef](#)] [[PubMed](#)]
21. Thierry, A.; Pogačić, T.; Weber, M.; Lortal, S. Production of flavor compounds by lactic acid bacteria in fermented foods. In *Biotechnology of Lactic Acid Bacteria: Novel Applications*, 2nd ed.; Mozzi, F., Raya, R.R., Vignolo, G.M., Eds.; John Wiley & Sons, Ltd.: West Sussex, UK, 2015; pp. 314–340. [[CrossRef](#)]
22. Chen, C.; Zhao, S.; Hao, G.; Yu, H.; Tian, H.; Zhao, G. Role of lactic acid bacteria on the yogurt flavour: A review. *Int. J. Food Prop.* **2017**, *20*, S316–S330. [[CrossRef](#)]
23. Steele, J.; Broadbent, J.; Kok, J. Perspectives on the contribution of lactic acid bacteria to cheese flavor development. *Curr. Opin. Biotechnol.* **2013**, *24*, 135–141. [[CrossRef](#)] [[PubMed](#)]
24. Cheng, H. Volatile flavor compounds in yogurt: A review. *Crit. Rev. Food Sci. Nutr.* **2010**, *50*, 938–950. [[CrossRef](#)] [[PubMed](#)]
25. Smid, E.J.; Kleerebezem, M. Production of aroma compounds in lactic fermentations. *Annu. Rev. Food Sci. Technol.* **2014**, *5*, 313–326. [[CrossRef](#)] [[PubMed](#)]
26. Farag, M.A.; Jomaa, S.A.; Abd El-Wahed, A.; El-Seedi, H.R. The many faces of kefir fermented dairy products: Quality characteristics, flavour chemistry, nutritional value, health benefits, and safety. *Nutrients* **2020**, *12*, 346. [[CrossRef](#)] [[PubMed](#)]
27. Han, H.; Wang, Y.; Meng, T.; Hou, B.; He, J.; Li, B.; Kong, C.; Wang, B. Unveiling metabolic mechanism of aroma-active compounds during yogurt fermentation through volatilomics, sensomics, and untargeted metabolomics analysis. *J. Dairy Sci.* **2026**, *109*, 8027–8042. [[CrossRef](#)] [[PubMed](#)]
28. Hadjimbei, E.; Botsaris, G.; Chrysostomou, S. Beneficial effects of yoghurts and probiotic fermented milks and their functional food potential. *Foods* **2022**, *11*, 2691. [[CrossRef](#)] [[PubMed](#)]
29. Mende, S.; Rohm, H.; Jaros, D. Influence of exopolysaccharides on the structure, texture, stability and sensory properties of yoghurt and related products. *Int. Dairy J.* **2016**, *52*, 57–71. [[CrossRef](#)]
30. Vinderola, G.; Cotter, P.D.; Freitas, M.; Gueimonde, M.; Holscher, H.D.; Ruas-Madiedo, P.; Salminen, S.; Swanson, K.S.; Sanders, M.E.; Cifelli, C.J. Fermented foods: A perspective on their role in delivering biotics. *Front. Microbiol.* **2023**, *14*, 1196239. [[CrossRef](#)] [[PubMed](#)]
31. Ibrahim, S.A.; Gyawali, R.; Awaisheh, S.S.; Ayivi, R.D.; Silva, R.C.; Subedi, K.; Aljaloud, S.O.; Siddiqui, S.A.; Krastanov, A. Fermented foods and probiotics: An approach to lactose intolerance. *J. Dairy Res.* **2021**, *88*, 357–365. [[CrossRef](#)] [[PubMed](#)]

32. Harlé, O.; Niay, J.; Parayre, S.; Nicolas, A.; Henry, G.; Maillard, M.B.; Valence, F.; Thierry, A.; Guédon, É.; Falentin, H.; et al. Deciphering the metabolism of *Lactobacillus delbrueckii* subsp. *delbrueckii* during soy juice fermentation using phenotypic and transcriptional analysis. *Appl. Environ. Microbiol.* **2024**, *90*, e01936–23. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Lucey, J.A.; Singh, H. Formation and physical properties of acid milk gels: A review. *Food Res. Int.* **1997**, *30*, 529–542. [\[CrossRef\]](#)
34. Hassan, A.N.; Ipsen, R.; Janzen, T.; Qvist, K.B. Microstructure and rheology of yogurt made with cultures differing only in their ability to produce exopolysaccharides. *J. Dairy Sci.* **2003**, *86*, 1632–1638. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Rehman, H.; Saipriya, K.; Singh, A.K.; Singh, R.; Meena, G.S.; Khethra, Y.; Sharma, H. A metabolomics approach to establish the relationship between the techno-functional properties and metabolome of Indian goat yoghurt. *Foods* **2024**, *13*, 913. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Cheng, S.; Wang, Y.; Li, B.; Hou, B.; Hung, W.; He, J.; Liang, C.; Jiang, Y.; Zhang, Y. Temperature-driven metabolic reprogramming in starter cultures impairs rheological properties and flavor release in fermented milk: A multi-omics approach. *Food Chem.* **2026**, *506*, 148035. [\[CrossRef\]](#) [\[PubMed\]](#)
37. An, M.; Zhao, Z.; Zhao, L.; Yang, J.; Gao, H.; Zhang, L.; Zhao, G.; Hou, B.; He, J.; Hung, W.L.; et al. Metabolic modulation of yogurt fermentation kinetics and storage stability by *Lactobacillus*-starter culture interactions. *Foods* **2025**, *14*, 2935. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Tian, H.; Hang, S.; Huang, N.; Yu, H.; Chen, C.; Ge, C. Strain-level variation in diacetyl production by *Lactiplantibacillus plantarum* reveals genetic drivers of flavor in fermented dairy. *J. Dairy Sci.* **2025**, *108*, 10689–10699. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Zhao, Z.; Shi, S.; Zhang, L.; An, M.; Wen, P.; Sang, Y.; Feng, H.; Hou, B.; He, J.; Hung, W.L.; et al. Metabolic modulation of yogurt fermentation kinetics and acidification by *Bifidobacterium*-starter culture interactions. *Front. Microbiol.* **2026**, *17*, 1724590. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Casarotti, S.N.; Monteiro, D.A.; Moretti, M.M.; Penna, A.L.B. Influence of the combination of probiotic cultures during fermentation and storage of fermented milk. *Food Res. Int.* **2014**, *59*, 67–75. [\[CrossRef\]](#)
41. Yang, Y.; Zhang, R.; Zhang, F.; Wang, B.; Liu, Y. Storage stability of texture, organoleptic, and biological properties of goat milk yogurt fermented with probiotic bacteria. *Front. Nutr.* **2023**, *9*, 1093654. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Nielsen, S.D.; Jakobsen, L.M.; Geiker, N.R.; Bertram, H.C. Chemically acidified, live and heat-inactivated fermented dairy yoghurt show distinct bioactive peptides, free amino acids and small compounds profiles. *Food Chem.* **2022**, *376*, 131919. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Arslan, B.N.; Döndaş, N.Y.; Koçhan, S.; Bulut, S.D.; Tamer, M.A.; Çelebioğlu, H.U.; Bodur, M.; Ağagündüz, D.; Tabanelli, G.; Barbieri, F.; et al. Functional fermented dairy products: A review of mechanisms, health potential, and technological challenges. *Front. Nutr.* **2026**, *13*, 1779688. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Awwad, F.; Al-Sumaidae, G.; Eltayeb, A.; Almazrouei, M.S.S.; Abdrabou, T.; Ayyash, M.M. Predicting functional bioactivities in fermented milk using deep learning on liquid chromatography-mass spectrometry metabolomics. *J. Dairy Sci.* **2026**, *109*, 3175–3194. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Barač, M.; Barač, N.; Taljić, I.; Sarić, Z. Lactose and type 2 diabetes: Nutritional and metabolic perspectives. *Mljekarstvo Dairy Experts J.* **2026**, *76*, 63–78. [\[CrossRef\]](#)
46. Tagliazucchi, D.; Martini, S.; Solieri, L. Bioprospecting for bioactive peptide production by lactic acid bacteria isolated from fermented dairy food. *Fermentation* **2019**, *5*, 96. [\[CrossRef\]](#)
47. Gunasekaran, V.; Das, D. Lipase fermentation: Progress and prospects. *Indian J. Biotechnol.* **2005**, *4*, 437–445.
48. Deeth, H.C. Lipoprotein lipase and lipolysis in milk. *Int. Dairy J.* **2006**, *16*, 555–562. [\[CrossRef\]](#)
49. Pan, D.D.; Wu, Z.; Peng, T.; Zeng, X.Q.; Li, H. Volatile organic compounds profile during milk fermentation by *Lactobacillus pentosus* and correlations between volatiles flavor and carbohydrate metabolism. *J. Dairy Sci.* **2014**, *97*, 624–631. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Tian, H.; Jing, Y.; Yu, H.; Huang, J.; Yuan, H.; Lou, X.; Wang, B.; Xu, Z.; Chen, C. Effect of alsD deletion and overexpression of nox and alsS on diacetyl and acetoin production by *Lactocaseibacillus casei* during milk fermentation. *J. Dairy Sci.* **2022**, *105*, 2868–2879. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Tiwari, S.; Kavitha, D.; Devi, P.B.; Shetty, P.H. Bacterial exopolysaccharides for improvement of technological, functional and rheological properties of yoghurt. *Int. J. Biol. Macromol.* **2021**, *183*, 1585–1595. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Pujato, S.A.; Mercanti, D.J.; Briggiler Marcó, M.; Capra, M.L.; Quiberoni, A.; Guglielmotti, D.M. Bacteriocins from lactic acid bacteria: Strategies for the bioprotection of dairy foods. *Front. Food Sci. Technol.* **2024**, *4*, 1439891. [\[CrossRef\]](#)
53. Abbasi, S.; Tan, J.S.; Ibrahim, T.A.T.; Bashokouh, F.; Ramakrishnan, N.R.; Mustafa, S.; Ariff, A.B. Fermentation factors influencing the production of bacteriocins by lactic acid bacteria: A review. *RSC Adv.* **2017**, *7*, 29395–29420. [\[CrossRef\]](#)
54. Agregán, R.; Echegaray, N.; Nawaz, A.; Hano, C.; Gohari, G.; Pateiro, M.; Lorenzo, J.M. Foodomic-based approach for the control and quality improvement of dairy products. *Metabolites* **2021**, *11*, 818. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Martínez, A.; Abanto, M.; Días, N.B.; Olate, P.; Pérez Nuñez, I.; Díaz, R.; Sepúlveda, N.; Paz, E.A.; Quiñones, J. Recent trends in food quality and authentication: The role of omics technologies in dairy and meat production. *Int. J. Mol. Sci.* **2025**, *26*, 4405. [\[CrossRef\]](#) [\[PubMed\]](#)

56. Xiao, X.; Fu, L.; Zhang, Z.; Tu, Z.; Shen, N.; Fan, S. Recent advances in integrating machine learning with omics approaches in food science and nutrition research. *J. Agric. Food. Chem.* **2025**, *73*, 29998–30025. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Sarkar, S.; Sha, S.P.; Ghatani, K. Metabolomics of ethnic fermented foods and beverages: Understanding new aspects through omic techniques. *Front. Sustain. Food Syst.* **2023**, *7*, 1040567. [\[CrossRef\]](#)
58. Settachaimongkon, S.; van Valenberg, H.J.; Smid, E.J. Metabolomics as an emerging strategy for the investigation of yogurt components. In *Yogurt in Health and Disease Prevention*; Shah, N.P., Ed.; Elsevier: Amsterdam, The Netherlands, 2017; pp. 427–449. [\[CrossRef\]](#)
59. Valdés, A.; Alvarez-Rivera, G.; Socas-Rodríguez, B.; Herrero, M.; Ibanez, E.; Cifuentes, A. Foodomics: Analytical opportunities and challenges. *Anal. Chem.* **2022**, *94*, 366–381. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Singh, N.; Barthwal, R.; Negi, A.; Aggarwal, S.; Kathuria, D.; Kumar, V.; Paul, M. Foodomics: Futuristic omic strategies to assess the impact of food nutrients on human health and gut microbiome. *Int. J. Food Sci. Technol.* **2024**, *59*, 4194–4212. [\[CrossRef\]](#)
61. Afsharia, R.; Pillidgea, C.J.; Diasb, D.A.; Osborna, A.M.; Gilla, H. Cheesomics: The future pathway to understanding cheese flavour and quality. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 33–47. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Shi, J.; Liu, Y.; Xu, Y.J. MS based foodomics: An edge tool integrated metabolomics and proteomics for food science. *Food Chem.* **2024**, *446*, 138852. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Trimigno, A.; Bøge Lyndgaard, C.; Atladóttir, G.A.; Aru, V.; Balling Engelsen, S.; Harder Clemmensen, L.K. An NMR metabolomics approach to investigate factors affecting the yoghurt fermentation process and quality. *Metabolites* **2020**, *10*, 293. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Zhang, Y.; Zhu, X.; Wang, N.; Liu, X.; Wang, L.; Ning, K. Synergy of traditional practices and modern technology: Advancing the understanding and applications of microbial resources and processes in fermented foods. *Trends Food Sci. Technol.* **2025**, *157*, 104891. [\[CrossRef\]](#)
65. O'Donnell, S.T.; Ross, R.P.; Stanton, C. The progress of multi-omics technologies: Determining function in lactic acid bacteria using a systems level approach. *Front. Microbiol.* **2020**, *10*, 3084. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Wusigale; Liu, K.; Wang, D.; Yang, C.; Liu, Y.; Altankhuyag, O.E.; Yao, G. Comparative genomics and untargeted metabolomics analysis of dairy-derived *Lactocaseibacillus rhamnosus* strains and their potential applications in dairy fermentation. *J. Dairy Sci.* **2025**, *108*, 6814–6827. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Balkir, P.; Kemahlioglu, K.; Yucel, U. Foodomics: A new approach in food quality and safety. *Trends Food Sci. Technol.* **2021**, *108*, 49–57. [\[CrossRef\]](#)
68. Liu, W.; Li, W.; Zheng, H.; Kwok, L.Y.; Sun, Z. Genomics divergence of *Lactococcus lactis* subsp. *lactis* isolated from naturally fermented dairy products. *Food Res. Int.* **2022**, *155*, 111108. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Moon, C.; Oh, W.Y.; Yeo, J. Proteomics and metabolomics for assessing metabolite changes, safety, and adulteration in milk products. *Food Sci. Biotechnol.* **2026**, *35*, 1433–1444. [\[CrossRef\]](#) [\[PubMed\]](#)
70. Ortea, I.; O'Connor, G.; Maquet, A. Review on proteomics for food authentication. *J. Proteom.* **2016**, *147*, 212–225. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Rizo, J.; Guillén, D.; Farrés, A.; Díaz-Ruiz, G.; Sánchez, S.; Wachter, C.; Rodríguez-Sanoja, R. Omics in traditional vegetable fermented foods and beverages. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 791–809. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Abril, A.G.; Quintela-Baluja, M.; Villa, T.G.; Calo-Mata, P.; Barros-Velázquez, J.; Carrera, M. Proteomic characterization of virulence factors and related proteins in *Enterococcus* strains from dairy and fermented food products. *Int. J. Mol. Sci.* **2022**, *23*, 10971. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Chen, L.; Zhang, C.; Shu, G. Proteomics analysis of proteolytic system expression of lactic acid bacteria in fermented goat milk with ACE inhibitory potential. *LWT* **2024**, *208*, 116717. [\[CrossRef\]](#)
74. Zhang, M.; Yao, M.; Lai, T.; Zhao, H.; Wang, Y.; Yang, Z. Response of *Lactiplantibacillus plantarum* NMGL2 to combinational cold and acid stresses during storage of fermented milk as analyzed by data-independent acquisition proteomics. *Foods* **2021**, *10*, 1514. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Dutta, B.; Lahiri, D.; Nag, M.; Abukhader, R.; Sarkar, T.; Pati, S.; Upadhye, V.; Pandit, S.; Amin, M.F.M.; Al Tawaha, A.R.M.S.; et al. Multi-omics approach in amelioration of food products. *Front. Microbiol.* **2022**, *13*, 955683. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Bai, L.; Zhang, Z.; Peng, X.; Gao, Z.; Zhao, Y.; Liang, K. Application of omics technology in the storage and transportation of agricultural products. *Front. Sustain. Food Syst.* **2023**, *7*, 1249199. [\[CrossRef\]](#)
77. Lamas, A.; Regal, P.; Vázquez, B.; Miranda, J.M.; Franco, C.M.; Cepeda, A. Transcriptomics: A powerful tool to evaluate the behavior of foodborne pathogens in the food production chain. *Food Res. Int.* **2019**, *125*, 108543. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Bassey, A.P.; Ye, K.; Li, C.; Zhou, G. Transcriptomic-proteomic integration: A powerful synergy to elucidate the mechanisms of meat spoilage in the cold chain. *Trends Food Sci. Technol.* **2021**, *113*, 12–25. [\[CrossRef\]](#)
79. Yohannis, E.; Teka, T.A.; Urugo, M.M. Advancements in foodomics: Transformative applications in enhancing food processing, ensuring quality, safety, traceability, and verifying authenticity. *Food Chem. Adv.* **2025**, *9*, 101138. [\[CrossRef\]](#)

80. Sun, L.; Zhang, Y.; Guo, X.; Zhang, L.; Zhang, W.; Man, C.; Jiang, Y. Characterization and transcriptomic basis of biofilm formation by *Lactobacillus plantarum* J26 isolated from traditional fermented dairy products. *LWT Food Sci. Technol.* **2020**, *125*, 109333. [\[CrossRef\]](#)
81. Wang, Y.; Zhao, H.; Zhang, H.; Hou, B.; Hung, W.; He, J.; Liang, C.; Li, B.; Man, C.; Jiang, Y.; et al. Metabolic and transcriptomic-based characterization of *Streptococcus salivarius* ssp. *thermophilus* snw fermentation in milk. *Foods* **2025**, *14*, 530. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Tian, H.; Huang, N.; Yao, W.; Yu, H.; Yu, B.; Chen, X.; Chen, C. Comparative transcriptomic analysis of the flavor production mechanism in yogurt by traditional starter strains. *J. Dairy Sci.* **2024**, *107*, 5402–5415. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Xiong, L.; Pei, J.; Bao, P.; Wang, X.; Guo, S.; Cao, M.; Kang, Y.; Yan, P.; Guo, X. The study of yak colostrum nutritional content based on foodomics. *Foods* **2023**, *12*, 1707. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Ijaz, Z.; Noor, Z.; Bibi, F.; Fayyaz, S.; Zafar, M.; Baig, A.; Siddiqua, A.; Zubair, M. Lipidomics and proteomics approaches in food composition analysis: A comprehensive overview. In *Novel Food Analysis*; Sarkar, T., Ed.; Humana: New York, NY, USA, 2026; pp. 369–389. [\[CrossRef\]](#)
85. Wang, Y.; Li, C.; Huang, J.; Zeng, Q.; Li, L.; Yang, P.; Wang, P.; Chu, M.; Luo, J.; Ren, F.; et al. Composition and structural characteristics of lipids in yak, buffalo, and cow colostrum based on untargeted lipidomics. *npj Sci. Food* **2025**, *9*, 37. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Meng, X.; Tang, K.; Shen, L.; Tao, K.; Zhao, J.; Yang, J.; Huang, Y.; Gu, Q.; Luo, Z.; Liu, Z.; et al. Multi-omics characterization of microbial, nutritional and flavor features and their correlations in traditional fermented yak milk from the Nagqu region of Tibet. *LWT Food Sci. Technol.* **2026**, *249*, 119435. [\[CrossRef\]](#)
87. Manis, C.; Casula, M.; Chessa, M.; Mangia, N.P.; Caboni, P. Lipidomic and metabolomic signatures of the traditional fermented milk product gioddu. *Dairy* **2025**, *6*, 61. [\[CrossRef\]](#)
88. Wang, Q.; Zhang, J.; Xia, Y.; Zha, M.; Li, J.; Jambal, T.; Dorjgotov, D.; Tseveen, S.; Chen, Y. Traditional fermented goat milk products in Mongolia: Analysis from the perspective of metagenomics to metabolomics. *J. Dairy Sci.* **2026**, *109*, 4811–4825. [\[CrossRef\]](#) [\[PubMed\]](#)
89. Cheng, S.; Li, W.; Yang, H.; Hou, B.; Hung, W.; He, J.; Liang, C.; Li, B.; Jiang, Y.; Zhang, Y.; et al. Integrated transcriptomics and metabolomics reveal changes during *Streptococcus thermophilus* JM66 fermentation in milk: Fermentation characteristics, flavor profile, and metabolic mechanism. *Food Res. Int.* **2025**, *203*, 115770. [\[CrossRef\]](#) [\[PubMed\]](#)
90. Ge, L.; Li, H.; Hong, Q.; Xu, X.; Wang, M.; Zhang, G.; Shi, H. Multiomics identified the nutritional improvement in LAB-Fermented goat milk. *J. Agric. Food. Chem.* **2025**, *73*, 31611–31621. [\[CrossRef\]](#) [\[PubMed\]](#)
91. Liu, Z.; Wang, Q.; Luo, S.; Xing, C.; Li, W.; Zeng, H.; Wang, Y. Multi-omics analysis elucidates flavor evolution and bioformation mechanisms of key aroma compounds in malty-aroma yogurt. *Foods* **2026**, *15*, 272. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Jia, W.; Liu, Y.; Shi, L. Integrated metabolomics and lipidomics profiling reveals beneficial changes in sensory quality of brown fermented goat milk. *Food Chem.* **2021**, *364*, 130378. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Wang, Y.; Wang, Y.; Qiu, S.; Wang, B.; Zeng, H. Metagenomic and flavoromic profiling reveals the correlation between the microorganisms and volatile flavor compounds in *Monascus*-fermented cheese. *Food Res. Int.* **2024**, *188*, 114483. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Shi, H.; An, F.; Lin, H.; Li, M.; Wu, J.; Wu, R. Advances in fermented foods revealed by multi-omics: A new direction toward precisely clarifying the roles of microorganisms. *Front. Microbiol.* **2022**, *13*, 1044820. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Becchi, P.P.; Rocchetti, G.; Lucini, L. Advancing dairy science through integrated analytical approaches based on multi-omics and machine learning. *Curr. Opin. Food Sci.* **2025**, *63*, 101289. [\[CrossRef\]](#)
96. Yuan, L.; Li, Y.; Wang, Z.; Xie, X.; Wu, Q. Gut microbiota-mediated antihypertensive effects of probiotic fermented milk: A multi-omics study. *J. Food Sci.* **2025**, *90*, e70654. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Cheng, S.; Zhang, Y.; Wang, Y.; Li, B.; Hou, B.; Hung, W.; He, J.; Liang, C.; Jiang, Y.; Zhang, Y. Integrated multi-omics elucidates the metabolic profile of *Lactobacillus delbrueckii* subsp. *bulgaricus* BG in fermented milk: Linking physicochemical changes, flavor biosynthesis, and transcriptional dynamics. *Food Sci. Hum. Wellness* **2026**, *16*. [\[CrossRef\]](#)
98. Amer, B.; Baidoo, E.E. Omics-driven biotechnology for industrial applications. *Front. Bioeng. Biotechnol.* **2021**, *9*, 613307. [\[CrossRef\]](#) [\[PubMed\]](#)
99. Araújo, A.M.; Carvalho, F.; Guedes de Pinho, P.; Carvalho, M. Toxicometabolomics: Small molecules to answer big toxicological questions. *Metabolites* **2021**, *11*, 692. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Arian, M.; Muth, T. Integrated multi-omics analyses of microbial communities: A review of the current state and future directions. *Mol. Omics* **2023**, *19*, 607. [\[CrossRef\]](#) [\[PubMed\]](#)
101. Wen, L.; Yang, L.; Chen, C.; Li, J.; Fu, J.; Liu, G.; Kan, Q.; Ho, C.T.; Huang, Q.; Lan, Y.; et al. Applications of multi-omics techniques to unravel the fermentation process and the flavor formation mechanism in fermented foods. *Crit. Rev. Food Sci. Nutr.* **2024**, *64*, 8367–8383. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Ji, J.; Jiang, X.; Song, P.; Yang, Q.; Sun, M.; Dong, Z.; Lu, Y.; Dou, S.; Dong, L. Multi-omics insights into microbial interactions and fermented food quality. *Microorganisms* **2025**, *13*, 2679. [\[CrossRef\]](#) [\[PubMed\]](#)

103. Chaudhary, A.; Bhalla, S.; Patiyal, S.; Raghava, G.P.; Sahni, G. FermFoodB: A database of bioactive peptides derived from fermented foods. *Heliyon* **2021**, *7*, e06668. [[CrossRef](#)] [[PubMed](#)]
104. Zinno, P.; Calabrese, F.M.; Schifano, E.; Sorino, P.; Di Cagno, R.; Gobbetti, M.; Parente, E.; Angelis, M.D.; Devirgiliis, C. FDF-DB: A database of traditional fermented dairy foods and their associated microbiota. *Nutrients* **2022**, *14*, 4581. [[CrossRef](#)] [[PubMed](#)]
105. Leek, J.T.; Scharpf, R.B.; Bravo, H.C.; Simcha, D.; Langmead, B.; Johnson, W.E.; Geman, D.; Baggerly, K.; Irizarry, R.A. Tackling the widespread and critical impact of batch effects in high-throughput data. *Nat. Rev. Genet.* **2010**, *11*, 733–739. [[CrossRef](#)] [[PubMed](#)]
106. Hasin, Y.; Seldin, M.; Lusis, A. Multi-omics approaches to disease. *Genome Biol.* **2017**, *18*, 83. [[CrossRef](#)] [[PubMed](#)]
107. Wilkinson, M.D.; Dumontier, M.; Aalbersberg, I.J.; Appleton, G.; Axton, M.; Baak, A.; Blomberg, N.; Boiten, J.W.; da Silva Santos, L.B.; Bourne, P.E.; et al. The FAIR guiding principles for scientific data management and stewardship. *Sci. Data* **2016**, *3*, 160018. [[CrossRef](#)] [[PubMed](#)]
108. Subramanian, I.; Verma, S.; Kumar, S.; Jere, A.; Anamika, K. Multi-omics data integration, interpretation, and its application. *Bioinf. Biol. Insights* **2020**, *14*, 1–24. [[CrossRef](#)] [[PubMed](#)]
109. Kwoji, I.D.; Aiyegoro, O.A.; Okpeku, M.; Adeleke, M.A. ‘Multi-omics’ data integration: Applications in probiotics studies. *npj Sci. Food* **2023**, *7*, 25. [[CrossRef](#)] [[PubMed](#)]
110. Misra, B.B.; Langefeld, C.; Olivier, M.; Cox, L.A. Integrated omics: Tools, advances and future approaches. *J. Mol. Endocrinol.* **2019**, *62*, R21–R45. [[CrossRef](#)] [[PubMed](#)]
111. Singh, A.; Shannon, C.P.; Gautier, B.; Rohart, F.; Vacher, M.; Tebbutt, S.J.; Lê Cao, K.A. DIABLO: An integrative approach for identifying key molecular drivers from multi-omics assays. *Bioinformatics* **2019**, *35*, 3055–3062. [[CrossRef](#)] [[PubMed](#)]
112. Adossa, N.; Khan, S.; Rytkönen, K.T.; Elo, L.L. Computational strategies for single-cell multi-omics integration. *Comput. Struct. Biotechnol. J.* **2021**, *19*, 2588–2596. [[CrossRef](#)] [[PubMed](#)]
113. Picard, M.; Scott-Boyer, M.P.; Bodein, A.; Périn, O.; Droit, A. Integration strategies of multi-omics data for machine learning analysis. *Comput. Struct. Biotechnol. J.* **2021**, *19*, 3735–3746. [[CrossRef](#)] [[PubMed](#)]
114. Shoaib, A.S.M.; Nishat, N.; Raasetti, M.; Arif, I. Integrative machine learning approaches for multi-omics data analysis in cancer research. *Int. J. Health Med.* **2024**, *1*, 26–39. [[CrossRef](#)]
115. Lu, J.; Zhang, W.; He, Y.; Jiang, M.; Liu, Z.; Zhang, J.; Zheng, L.; Zhou, B.; Luo, J.; He, C.; et al. Multi-omics decodes host-specific and environmental microbiome interactions in sepsis. *Front. Microbiol.* **2025**, *16*, 1618177. [[CrossRef](#)] [[PubMed](#)]
116. Olowolayemo, A.; Souag, A.; Sirlantzis, K.; Turner, S.; Wilson, C. A review of multi-omics integration techniques across five machine learning method families. *Bioinf. Adv.* **2026**, *6*, vbag108. [[CrossRef](#)] [[PubMed](#)]
117. Argelaguet, R.; Velten, B.; Arnol, D.; Dietrich, S.; Zenz, T.; Marioni, J.C.; Buettner, F.; Huber, W.; Stegle, O. Multi-omics factor analysis—A framework for unsupervised integration of multi-omics data sets. *Mol. Syst. Biol.* **2018**, *14*, e8124. [[CrossRef](#)] [[PubMed](#)]
118. Wang, B.; Mezlini, A.M.; Demir, F.; Fiume, M.; Tu, Z.; Brudno, M.; Haibe-Kains, B.; Goldenberg, A. Similarity network fusion for aggregating data types on a genomic scale. *Nat. Methods* **2014**, *11*, 333–337. [[CrossRef](#)] [[PubMed](#)]
119. Muñoz-Redondo, J.M.; Puertas, B.; Pereira-Caro, G.; Ordóñez-Díaz, J.L.; Ruiz-Moreno, M.J.; Cantos-Villar, E.; Moreno-Rojas, J.M. A statistical workflow to evaluate the modulation of wine metabolome and its contribution to the sensory attributes. *Fermentation* **2021**, *7*, 72. [[CrossRef](#)]
120. Afshari, R.; Pillidge, C.J.; Dias, D.A.; Osborn, A.M.; Gill, H. Biomarkers associated with cheese quality uncovered by integrative multi-omic analysis. *Food Control* **2021**, *123*, 107752. [[CrossRef](#)]
121. Herraiz-Gil, S.; de Arriba, M.D.C.; Escamez, M.J.; Leon, C. Multi-omic data integration in food science and analysis. *Curr. Opin. Food Sci.* **2023**, *52*, 101049. [[CrossRef](#)]
122. Le, T.H. Next-generation foodomics: Integrated multi-omics approaches for structural and functional profiling of plant-based proteins and polyphenols. *J. Food Compos. Anal.* **2025**, *148*, 108634. [[CrossRef](#)]
123. Santorsola, M.; Lescai, F. The promise of explainable deep learning for omics data analysis: Adding new discovery tools to AI. *New Biotechnol.* **2023**, *77*, 1–11. [[CrossRef](#)] [[PubMed](#)]
124. Wu, X.; Jia, W. Multimodal deep learning as a next challenge in nutrition research: Tailoring fermented dairy products based on cytidine diphosphate-diacylglycerol synthase-mediated lipid metabolism. *Crit. Rev. Food Sci. Nutr.* **2024**, *64*, 12272–12283. [[CrossRef](#)] [[PubMed](#)]
125. Singh, A.; Kumar, S. Exploring the functionality of microbes in fermented foods: Technological advancements and future directions. *Fermentation* **2025**, *11*, 300. [[CrossRef](#)]
126. Jiang, L.; Lu, Y.; He, Q. Unlocking the microbial mechanisms in fermented bean products: Advances and future directions in multi-omics and machine learning approaches. *Crit. Rev. Food Sci. Nutr.* **2026**, *66*, 1364–1386. [[CrossRef](#)] [[PubMed](#)]
127. Bansal, S.; Rodriguez, C.Z.; Thompson-Witrick, K.A.; Wang, Y.; Taft, D.H.; Zhang, B. Machine learning-powered multi-omics for food microbiology and smarter food safety. *Trends Food Sci. Technol.* **2025**, *163*, 105145. [[CrossRef](#)]

128. Tan, M.S.; Cheah, P.L.; Chin, A.V.; Looi, L.M.; Chang, S.W. A review on omics-based biomarkers discovery for Alzheimer's disease from the bioinformatics perspectives: Statistical approach vs machine learning approach. *Comput. Biol. Med.* **2021**, *139*, 104947. [\[CrossRef\]](#) [\[PubMed\]](#)
129. Maione, C.; Barbosa, F.; Barbosa, R.M. Predicting the botanical and geographical origin of honey with multivariate data analysis and machine learning techniques: A review. *Comput. Electron. Agric.* **2019**, *157*, 436–446. [\[CrossRef\]](#)
130. Ballard, J.L.; Wang, Z.; Li, W.; Shen, L.; Long, Q. Deep learning-based approaches for multi-omics data integration and analysis. *BioData Min.* **2024**, *17*, 38. [\[CrossRef\]](#) [\[PubMed\]](#)
131. Sarker, I.H. Deep learning: A comprehensive overview on techniques, taxonomy, applications and research directions. *SN Comput. Sci.* **2021**, *2*, 420. [\[CrossRef\]](#) [\[PubMed\]](#)
132. Li, C.; Wang, X.; Liu, H.; Zhu, D. Applications and advances of deep learning in food microbiology: From data to intelligent analysis. *Trends Food Sci. Technol.* **2026**, *172*, 105687. [\[CrossRef\]](#)
133. Rugji, J.; Erol, Z.; Taşçı, F.; Musa, L.; Hamadani, A.; Gündemir, M.G.; Karalliu, E.; Siddiqui, S.A. Utilization of AI–reshaping the future of food safety, agriculture and food security—A critical review. *Crit. Rev. Food Sci. Nutr.* **2025**, *65*, 5136–5180. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Saetae, D. Machine learning-based prediction of microbial growth and acidification in yogurt fermentation at industrial temperatures. *LWT Food Sci. Technol.* **2025**, *231*, 118326. [\[CrossRef\]](#)
135. Becchi, P.P.; Rocchetti, G.; García-Pérez, P.; Michelini, S.; Pizzamiglio, V.; Lucini, L. Untargeted metabolomics and machine learning unveil quality and authenticity interactions in grated Parmigiano Reggiano PDO cheese. *Food Chem.* **2024**, *447*, 138938. [\[CrossRef\]](#) [\[PubMed\]](#)
136. Yang, H.; Liu, A.; Du, W.; Liu, Z.; Wang, G.; Yi, H.; Zhang, L.; Liu, T. Machine learning-guided identification and synergistic analysis of key aroma compounds in creamy-type *Streptococcus thermophilus*-fermented milk. *Food Biosci.* **2026**, *78*, 108556. [\[CrossRef\]](#)
137. Chen, Y.; Xing, Z.; Sheng, J.; Liu, X.; Ding, W.; Chen, X. Trends in the application of multiomics based on machine learning in the development of probiotics. *J. Agric. Food. Chem.* **2026**, *74*, 8070–8084. [\[CrossRef\]](#) [\[PubMed\]](#)
138. Boateng, E.Y.; Otoo, J.; Abaye, D.A. Basic tenets of classification algorithms K-nearest-neighbor, support vector machine, random forest and neural network: A review. *J. Data Anal. Inf. Process.* **2020**, *8*, 341–357. [\[CrossRef\]](#)
139. Ye, J.; Zhao, J.; Ye, K.; Xu, C. How to Build a Graph-Based Deep Learning Architecture in Traffic Domain: A Survey. *IEEE Trans. Intell. Transp. Syst.* **2020**, *23*, 3904–3924. [\[CrossRef\]](#)
140. Shaygan, M.; Meese, C.; Li, W.; Zhao, X.G.; Nejad, M. Traffic prediction using artificial intelligence: Review of recent advances and emerging opportunities. *Transp. Res. Part C Emerg. Technol.* **2022**, *145*, 103921. [\[CrossRef\]](#)
141. Zapata-Cortes, O.; Arango-Serna, M.D.; Zapata-Cortes, J.A.; Restrepo-Carmona, J.A. Machine learning models and applications for early detection. *Sensors* **2024**, *24*, 4678. [\[CrossRef\]](#) [\[PubMed\]](#)
142. Zhou, J.; Gan, L.; Du, L.; Liu, X.; Song, P.; Tang, X.; Wang, K.; Yang, B.; Chen, T.; He, Y.; et al. Intelligent monitoring technologies for food fermentation processes: Transformation from traditional experience to multimodal approaches and challenges. *Food Sci. Biotechnol.* **2026**. [\[CrossRef\]](#)
143. Zhang, D.; Jia, C.; Sun, D.; Gao, C.; Fu, D.; Cai, P.; Hu, Q.N. Data-driven prediction of molecular biotransformations in food fermentation. *J. Agric. Food. Chem.* **2023**, *71*, 8488–8496. [\[CrossRef\]](#) [\[PubMed\]](#)
144. Kim, Y.; Lee, S.H.; Jung, M.J.; Lee, J.; Kim, Y.B.; Hong, Y.S.; Whon, T.W. Strain-specific metabolic endpoints and predictive phase classification in gnotobiotic kimchi fermentation. *Food Chem.* **2026**, *504*, 147886. [\[CrossRef\]](#) [\[PubMed\]](#)
145. Zhou, Z.; Hu, M.; Salcedo, M.; Gravel, N.; Yeung, W.; Venkat, A.; Guo, D.; Zhang, J.; Kannan, N.; Li, S. XAI meets biology: A comprehensive review of explainable AI in bioinformatics applications. *arXiv* **2023**, arXiv:2312.06082. [\[CrossRef\]](#)
146. Hussein, A.; Prasad, M.; Braytee, A. Explainable ai methods for multi-omics analysis: A survey. *arXiv* **2024**, arXiv:2410.11910. [\[CrossRef\]](#)
147. Arrighi, L.; de Moraes, I.A.; Zullich, M.; Simonato, M.; Barbin, D.F.; Barbon Junior, S. Explainable artificial intelligence techniques for interpretation of food models: A review. *Artif. Intell. Rev.* **2026**, *59*, 176. [\[CrossRef\]](#)
148. Du, L.; Zhou, J.; Tang, Y.; Liu, X.; Zhong, J.; Yang, B.; He, Y.; Tuo, X.; Du, H. Intelligent recognition of the fermentation stage of baijiu based on multi-dimensional data fusion and interpretable machine learning. *Food Res. Int.* **2026**, *229*, 118451. [\[CrossRef\]](#) [\[PubMed\]](#)
149. Ribeiro, M.T.; Singh, S.; Guestrin, C. “Why should I trust you?” Explaining the predictions of any classifier. In Proceedings of the 2016 Conference of the North American Chapter of the Association for Computational Linguistics: Demonstrations, San Diego, CA, USA, 12–17 June 2016; pp. 1135–1144.
150. Moon, S.; Lee, H. MOMA: A multi-task attention learning algorithm for multi-omics data interpretation and classification. *Bioinformatics* **2022**, *38*, 2287–2296. [\[CrossRef\]](#) [\[PubMed\]](#)
151. Jain, S.; Wallace, B.C. Attention is not explanation. In Proceedings of the 2019 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies, Minneapolis, MN, USA, 2–7 June 2019; Volume 1, pp. 3543–3556.

152. Kanwal, N.; Zhang, M.; Khan, S.; Batool, U. AI-Driven precision fermentation: From restaurant food waste to sustainable protein production. *Food Bioprocess Technol.* **2025**, *18*, 8354–8379. [[CrossRef](#)]
153. Adeleke, I.; Adebo, O.A.; Nwulu, N. Leveraging IoT and machine learning for smart fermentation of amasi: A predictive framework for acidity control. *J. Agric. Food Res.* **2025**, *24*, 102409. [[CrossRef](#)]
154. Adeleke, I.; Nwulu, N.; Adebo, O.A. A digital twin approach for real-time monitoring of amasi acidity using non-invasive computer vision, IoT, and machine learning. *Food Control* **2026**, *182*, 111809. [[CrossRef](#)]
155. Lecomte, M.; Cao, W.; Aubert, J.; Sherman, D.J.; Falentin, H.; Frioux, C.; Labarthe, S. A digital twin of bacterial metabolism during cheese production. *bioRxiv* **2023**, bioRxiv:2023.05.05.539417. [[CrossRef](#)]
156. Lundberg, S.M.; Lee, S.I. A unified approach to interpreting model predictions. *Advances in neural information processing systems, 31st Conference on Neural Information Processing Systems (NIPS 2017)*, Long Beach, CA, USA, 4–9 December 2017; pp. 4768–4777.

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