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Development of Phenolic-Rich Functional Foods by Lactic Fermentation of Grape Marc: A Review

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ABSTRACT

Grape marc is a waste product produced during the winemaking process. The enormous volume of wine production worldwide creates a significant amount of grape marc each year. It is rich in nutrients and has excellent antioxidant properties. Lactic acid fermentation is a popular food preparation method, and by using grape marc as a substrate for fermentation, the pomace is preserved and the health benefits are improved, thus being a potentially valuable method that allows efficient management of pomace. This review describes the nutritional value of grape marc, the conditions necessary to ferment grape marc using lactic acid bacteria, and the characteristic chemical changes that occur during fermentation. Furthermore, it describes the research prospects for producing novel functional foods or products by interacting strains with phytochemicals in grape marc. More research is needed to optimize the use of starter cultures, improve fermentation efficiency, and develop sustainable processes.

KEYWORDS

Grape marc; lactic acid fermentation; functional food; food waste; bioactive compounds; polyphenols

Introduction

Grapes consistently rank in the top five of all fruits regarding total global production.[1] According to the Food and Agriculture Organisation of the United Nations (FAO), in 2021, approximately 73.52 million tons of grapes were produced.[1] Although global epidemics and other factors led to deficient wine production in 2021, the International Organization of Vine and Wine (OIV) indicates that approximately 250.3 million hectoliters of wine were still produced globally.[2] During the winemaking process, fermenting the juice extraction for white wines or pressing grapes after fermentation for red wines results in solid waste, namely grape marc (GM) or grape pomace. The GM accounts for almost 25% of the mass of pressed grapes and consists mainly of stems, skins, disrupted cells from grape pulp, and the seeds remaining after the crushing and pressing steps.[3] It contains alcohol, polyphenols, tannins, pigments, unfermented sugars, and other valuable compounds.

The large amount of soluble sugars contained in GM could be used in ethanol fermentation to produce a beverage known as grape spirit.[4] Furthermore, by fermenting these residual sugars, the economic value of GM can be augmented through the production of industrial ethanol, which finds applications in cosmetic and pharmaceutical industries. Additionally, by producing bioethanol, GM represents a competitive and valuable alternative to fossil fuels, potentially fostering a more sustainable energy landscape.[3] Grape marc stands as a promising source for the recovery of bioactive substances, owing to its rich content of polyphenols, such

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as anthocyanins, catechins, and flavonols.[5] Consequently, GM can be employed in the production of nutraceuticals and functional foods through the enhancement of health-promoting compound concentrations, the reduction of undesirable ingredients, and the incorporation of innovative ingredients possessing advantageous technical properties.[6] Grape marc has been previously considered as an animal feed additive[7]; however, its relatively high polyphenol content may lower digestibility. This is because polyphenols can negatively influence the activity of cellulolytic and proteolytic enzymes, as well as suppress the growth of rumen microorganisms.[7] Another promising application for GM involves its use as an organic soil amendment, owing to its rich organic matter and substantial nutrient content.[8] Nonetheless, its direct application to soil could generate phytotoxic and antimicrobial effects, leading to detrimental consequences on plant growth due to the release of tannins and other polyphenols.[7] Addressing the proper treatment, disposal, or reuse of GM to prevent negative environmental impacts emerges as a topic of considerable interest for both the scientific community and producers. Despite GM's impressive potential for developing numerous value-added products, the wide-scale adoption of advanced technologies to efficiently utilize this potential has yet to be evident in wineries and related industries.

Fermentation, a time-honored and cost-efficient method of food preparation, entails a preservation process that hinges on the growth and metabolism of microorganisms. This technique can be bifurcated into two principal classifications: aerobic fermentation, comprising fungal and alkaline processes, and anaerobic fermentation, encompassing alcoholic and lactic acid processes.[9] Throughout the fermentation process, microorganisms decompose fermentable carbohydrates and produce organic acids, carbon dioxide, alcohol, as well as antimicrobial substances called bacteriocins. These by-products play a critical role in augmenting food safety by suppressing foodborne pathogens and neutralizing harmful microorganisms.[10] The fermentation process not only extends the shelf life of food products but also enhances their organoleptic properties, protein and carbohydrate digestibility, and the bioavailability of vitamins and minerals.[11] Therefore, scientists are increasingly interested in fermentation processes and fermentation products. The microorganisms that facilitate fermentation have also garnered attention due to their recently discovered association with numerous health benefits.[12] Among these microorganisms, lactic acid bacteria (LAB) have received substantial focus in the fermentation process. These bacteria are known to synthesize vitamins and minerals, produce bioactive peptides using enzymes such as proteases and peptidases, and eliminate several non-nutrients. Moreover, the bioactive peptides generated by LAB have been acknowledged for their health-promoting properties.[12]

Using fruits as substrate and fermentation with autochthonous or allochthonous LAB (such as *Lactiplantibacillus plantarum*, *Lacticaseibacillus rhamnosus*, and other *Lactobacillus* species) is a technical option for processing GM, while fruits are also significant carriers for probiotics.[13] During the fermentation process, microbial enzymes interact with several phytochemicals of fruits to produce new derivative compounds that affect the aroma and functionality of fermented products. Additionally, fermentation processes substantially decrease the sugar content in fruit beverages, which in turn enhances their nutritional value and prolongs their shelf life[13] (Fig. 1). Developing novel probiotic beverages signifies a promising approach to catering to the needs of consumers with lactose intolerance or those who adhere to vegan or vegetarian diets. Furthermore, such innovations hold immense potential in the global functional food market.

There have been several studies on GM conversion using fermentation technology,[4] including bioenergy production, enzyme extraction, and single cell protein production. There are also numerous studies on the fermentation of fruit substrates to obtain fermented food products,[13] however, there is a lack of research on the conversion of GM as a substrate into functional products using LAB fermentation. This review describes the necessary conditions for fermenting GM using LAB and the

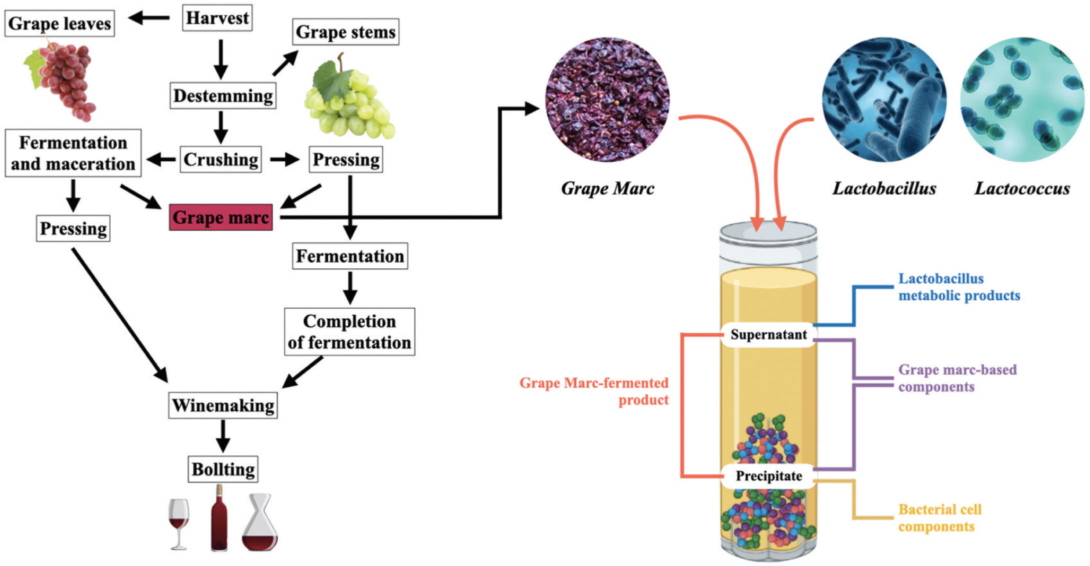


Figure 1. Production diagram and lactic acid fermentation of grape marc.

research prospects for producing novel functional foods or products by interacting strains with bioactive phytochemicals in GM.

Components of grape marc

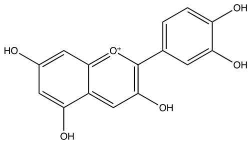
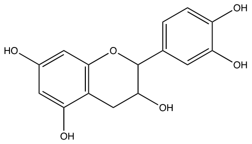
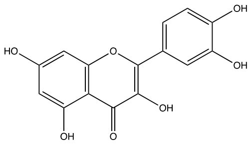
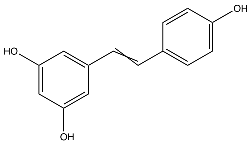
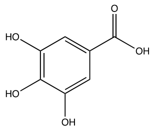
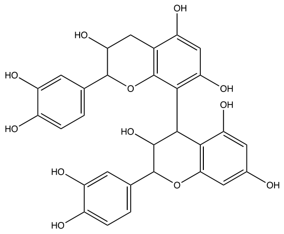
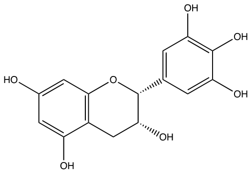
Grapes are an abundant source of various components, some of which are extracted during the winemaking process. The residual GM left behind is a rich source of phytochemicals, including a diverse range of phenolic compounds, pigments, and antioxidants.[14] Additionally, grape marc comprises other valuable constituents such as fatty acids, proteins (18.8% *w/w*. grape skin only[15]), carbohydrates (reducing sugars 1.5 ± 0.3% *w/w*[16]), minerals, moisture (73.6 ± 2.6% *w/w*[16]), and lignocellulosic materials (cellulose 20.8% *w/w;* Hemicelluloses 12.5% *w/w*. grape skin only[15]). These components render grape marc a highly promising candidate for further exploration and exploitation in various applications.[17]

Polyphenols

Polyphenol is a secondary metabolite of plants. It is a kind of bioactive compound with antioxidant, anticancer, antifungal, and antibacterial capacities that benefit human health.[18] Tannins or condensed tannins commonly refer to polyphenols (proanthocyanidins) found in the skin and seed of grapes, whereas anthocyanins, the pigments in the skin of red grapes, are identified as monomeric flavonoids.[19] The phenolic compounds extracted from GM predominantly consist of gallic acid, catechin, and epicatechin. Additionally, other compounds such as hydroxytyrosol, tyrosol, cyanidin glycosides, and various phenolic acids, including caffeic, procatechuic, syringic, vanillic, *o*-coumaric, and *p*-coumaric acids, have been identified.[20] Approximately 60% to 70% of all retrievable polyphenols found in grapes are located within the seeds, contributing to about 5% to 8% of the overall seed mass.[21] Extractable phenolics represent 10–11% of GM's dry weight (DW). Polyphenols with essential physiological functions isolated from GM are summarised in Table 1.

The composition of polyphenols exhibits a high degree of diversity, influenced by factors such as grape variety, climatic conditions, geographical location, and the level of grape ripeness. Due to the complex composition of GM polyphenols, it is not easy to extract effective bioactive substances. Aliona

Table 1. Polyphenol with important bioactive properties isolated from grape marc.

Compound Name	Classification	Structure	Molecular Formula	Function
Cyanidin	Anthocyanidin		$C_{15}H_{11}O_6^+$	Oxygen radical sequestration
Catechin/ Epicatechin	Catechin, flavan-3-ol		$C_{15}H_{14}O_6$	Anticancer, antisclerotic, antidiabetic, free radical sequestration
Quercetin	Flavonol		$C_{15}H_{10}O_7$	Anti-inflammatory, antiallergic, anticancer, antioxidant
Resveratrol	Fitoalexin stilbene		$C_{14}H_{12}O_3$	Antioxidant, antimicrobial, anticancer anti-inflammatory, blood glucose lowering
Gallic acid	Phenolic acid		$C_7H_6O_5$	Antioxidant, anticancer, anti-inflammatory, antimicrobial
Proanthocyanidin B2	Proanthocyanidin		$C_{30}H_{26}O_{12}$	Improvement of dyslipidemia, hyperglycemia, oxidative stress
Epigallocatechin	Catechin		$C_{15}H_{14}O_7$	Antioxidant, cancer chemoprevention, cardiovascular health improvement, weight loss promotion

Ghendov-Mosanu et al. characterized a large amount of proanthocyanidin B2 (824.73 μg/100 g DW) in hydroethanolic GM extract at 60% (*v/v*) and extraction temperature of 65°C.[22] Furthermore, gallic acid (104.84 μg/100 g DW), catechin (72.04 μg/100 g DW), proanthocyanidin B1 (71.51 μg/100 g DW), ferulic acid (44.09 μg/100 g DW) and methyl ferulate (39.78 μg/100 g DW) were also detected in GM. Research on the phenolic content and antioxidant capacity in GM obtained from the winemaking process of four popular grape varieties in Brazil (Cabernet Sauvignon, Merlot, Bordeaux, and Isabel) disclosed that, among all varieties, catechins represented the highest concentration of non-anthocyanin compounds detected in GM (150.16 mg/100 g); Cabernet Sauvignon marc had the highest total phenolic content (75 mg/g), and the Bordeaux variety had the most abundant total anthocyanin content.[23] Due to the prolonged contact between skins and seeds with the fermentation broth during red winemaking, red grape marc tends to retain a smaller proportion of the initial grape polyphenols compared to white grape marc throughout the winemaking process. On the contrary, the white grape skins barely come into contact with the fermentation broth during winemaking, thus the white GM retains the initial grape polyphenols.[24] Red grape skins have been found to possess a higher concentration of hydroxycinnamic acid and anthocyanins in comparison to white grape skins. In contrast, the levels of catechins, proanthocyanidin dimers, and total flavonols are significantly lower in red grape skins.[25] The most predominant phenolic compound present in white grape varieties is flavan-3-ol.[26]

Tannins are one of the polyphenols that have been attracting attention in GM. It contains aromatic rings with hydroxyl groups, which bring them significant chemical activity and lead them to form complexes with other macromolecules, like carbohydrates[27] or bacterial cell membranes.[28] Nevertheless, it is mainly involved in the complexation and precipitation of proteins.[29] Tannins have impressive antioxidant properties and are widely utilized in both the food and pharmaceutical industries. Research has demonstrated their potential in preventing diseases associated with oxidative stress, including cardiovascular disease, cancer, and osteoporosis.[30] Among various phenolic compounds found in grapes, condensed tannins (proanthocyanidins) are predominantly present in the skin and seeds. Based on dry weight, condensed tannins account for 20–51% (*w/w*) in GM.[31]

Resveratrol (3, 5, 4'–trihydroxystilbene) (RES) is another essential phenolic compound found in grape skins and seeds. Despite being identified in over 70 plant species, grapes remain the principal dietary source of RES.[32] The trans-RES content exhibits a range of 1.11 to 12.3 mg/100 g DW in grape skins, 8.64 ± 4.5 mg/100 g DW in white grape skins, and 1.42 ± 0.18 mg/100 g DW in white grape seeds.[33] Although a portion of RES from grapes is transferred to wine during the maceration process, a significant amount of RES still remains in GM.[34] This compound has numerous properties, including antiglycation, antioxidant stress, anti-inflammatory, anti-neurodegenerative, anticancer, and anti-aging activities.[32] It has been of interest for its chemopreventive and therapeutic effects on various diseases, especially in the anticancer area.[35,36]

Moreover, similar to other plant materials, GM contains a certain quantity of non-extractable phenolic compounds (NEP). A large proportion of high-molecular-weight proanthocyanidins and polyphenols interact with proteins or cell wall polysaccharides, rendering them insoluble in the organic solvents typically utilized for extraction. As a result, numerous polyphenols form complexes with fibers, which also cannot be directly extracted.[37,38] The quantification of NEP necessitates the hydrolysis of GM residues to liberate phenolic compounds bound to cell walls or proteins. This process occurs subsequent to the extraction of soluble polyphenols.[39] Non-extractable phenolic compounds content varies significantly among different grape varieties, for example, red GM from the Cencibel variety possesses a high concentration of up to 67 mg/g DW, whilst white GM from the Thompson variety (no nucleus), exhibits a significantly lower 1.68 mg/g DW.[40] This variation underscores the importance of taking grape variety into account when examining the effects of NEP levels in GM.

Carbohydrates

Carbohydrates represent a significant portion of GM. Based on dry weight, 31–54% *w/w* of GM is a carbohydrate, of which 47–80% is soluble in water.[41] After pressing and processing, the residual carbohydrates remaining in GM were mainly water-soluble monosaccharides, oligosaccharides, polysaccharides, and water-insoluble structural polysaccharides from the cell wall.[42] Soluble carbohydrates can be easily extracted and directly utilized as raw substrates for fermentation, whereas cell wall polysaccharides require pre-treatment and saccharification for release. In white GM, water-soluble carbohydrates represent approximately one-third of the dry weight (37.6% *w/w*) and 70% of the total carbohydrate content.[41] Conversely, the proportion of soluble carbohydrates in red GM is considerably lower, at a mere 4.6% (*w/w*).[41] This relatively low content of water-soluble carbohydrates in red GM is likely due to the winemaking process, wherein red GM is in contact with juice for several days to enhance the wine's color and sensory attributes. Over this period, partial fermentation of carbohydrates occurs. Pierangelo Rondeau et al.[31] used the HPAEC-PAD to determine the soluble fraction of GM after sulfuric acid hydrolysis and to estimate its monosaccharide content. The obtained glucose and xylose yields revealed that GM contains considerable amounts of glucans and xyloglucans.

Dietary fiber has beneficial physiological effects, including defecation, decreased blood cholesterol, and glucose.[43] Grape marc contains abundant total dietary fiber (TDF). The TDF in white GM was 716 g/kg DW,[44] and three-quarters of the total dry matter in red GM was TDF.[45] The proportion of soluble dietary fiber (SDF) in GM relative to TDF was large, approximately 14.5%, for both red and white grapes.[44,45] This may be attributed to the residual pulp and seeds from the winemaking process and fermentation before the pressing process during winemaking.[44] Pectin is a significant component of SDF in GM, accounting for about 60%.[45] Insoluble dietary fiber is mainly provided by cellulose, hemicellulose, and lignin, primarily present in the stem.[4] The process of lignification results in significant modifications to the structure of secondary cell walls, leading to their impregnation with lignin. In particular, stems, which possess a high proportion of these secondary walls, undergo a transformation wherein water within the cell wall is progressively replaced by lignin deposition. This phenomenon of lignification fundamentally alters the physical properties of the cell wall.[44] These large amounts of lignocellulosic polysaccharides contained in GM could be hydrolyzed by acid to produce glucose, xylose, and other monosaccharides.[46] Subsequently, they serve as fermentation substrates to produce various products, including lactic acid, antioxidants, biosurfactants, enzyme, protein and anti-allergens.[4]

Protein and fatty acid

Grape marc contains a certain amount of protein and fatty acids, which must be adequately studied due to the challenge of extraction and utilization limitations. One of the main contributors is grape seeds.

Grape seeds are a notable source of oleic and linoleic acids, with content ranging from 17.8% to 26.5% and 60.1% to 70.1%, respectively.[47] Notably, grape seed oil possesses an unsaturation exceeding 86%, comprising entirely of essential fatty acids.[48] The total tocopherol concentration in the oil reaches even approximately 454 mg/kg.[48] Moreover, β-carotene[49] and the amounts of phytosterols[47] are also significant components. The fatty acid composition of grape seed oil depends on its variety and maturity.[48]

Despite containing approximately 11–13% protein, grape seeds cannot be considered a primary source of essential protein such as nuts and legumes.[50] The overall protein content and amino acid composition of grape seed are highly dependent on various factors, such as the grape variety, origin, and fertilization conditions. Nonetheless, amino acid analysis has indicated a high concentration of essential amino acids, particularly glycine, glutamic acid and aspartic acid, which had the most abundant representation in GM.[51] The most prominent protein component in grape seed isolate is globulin-link protein, which entails greater solubility, emulsification and emulsion stability than soy isolates, whereas its foaming ability is unsatisfactory.[52] However, due to the significant interaction between protein and tannins, the protein digestibility is lowered,[53] and some proteins are deemed indigestible. Additional studies are necessary to determine the absorption of grape seed proteins when combined with procyanidins in the gastrointestinal tract.

Lactic acid fermentation of grape marc

Lactic acid bacteria fermentation is an ancient technique to extend the shelf life of perishable foods, preserving them while minimizing changes in their properties.[54] Nowadays, the demand for functionality, freshness, nutritional value, and healthiness continues to grow. The growth of lactic acid fermentation has been further fueled by the increasing popularity of vegetarianism and the rise in lactose intolerance. In light of this, the fermentation of fruit substrates by LAB presents a promising alternative solution to meet these demands and promote fruit consumption.[55] Research into the design of lactic acid fermented fruit juices and their functions has continued to expand in recent years.

Lactic acid fermentation is a straightforward, valuable, cost-effective, and sustainable process that offers numerous benefits. Firstly, it facilitates the formation of organic acids, ethanol, and antimicrobial compounds, all of which significantly enhance the safety of foods and promote their preservation. Secondly, it enhances the nutritional value of food products, thereby making them more nutritious for consumption. Lastly, it helps to maintain the organoleptic qualities of food products, ensuring that their texture, appearance, and flavor remain intact.[21] Fruit fermentation allows for "spontaneous fermentation" using native lactic acid microbiota, including *Lactobacillus* spp., *Leuconostoc spp*., *Fructobacillus spp*., and *Pediococcus* spp. The fermentation process needs to be carried out under favorable conditions in terms of anaerobic, humidity, salt concentration, and temperature.

Whether grape marc fulfills the conditions for lactic acid fermentation

In the case of fermented foods on plant substrates, it is imperative that the starter culture is versatile and adaptable to the current challenging conditions. Various factors influence the growth and acidification of lactic acid bacteria in plant substrates, including the concentration of fermentable carbohydrates, the acidic environment and buffering capacity, indigestible substances like fiber, lignin, oligofructose, tannins and polyphenols.[13]

There are also some studies using LAB to ferment GM to produce functional products with favorable results.[56,57] Grape marc contains abundant carbohydrates, such as glucose and fructose,[17] which can be fermented by LAB to produce lactic acid. Additionally, GM contains sufficient other compounds, including vitamins, minerals, antioxidants,[14] and also some autochthonous starter cultures,[58] which all can be beneficial for fermentation. Several pigments in the GM, for instance, anthocyanins[19] and β-carotene,[49] behave as antioxidant compounds in the body and assist in the elimination of free radicals associated with aging and degenerative diseases such as cancer, and arthritis.[59] However, lactic acid fermentation of GM is less common than in other fruits. This is because it contains high amounts of tannins,[14] which can inhibit the growth and metabolism of LAB.[13] Also, GM contains significant amounts of phenolic compounds[14] that can affect the character of the final product, like color, taste, and astringency.

Using selected autochthonous starter cultures in fermented foods guarantees better yields, enhances the product's nutritional, organoleptic, and rheological properties, and ensures a longer shelf life than commercial or allochthonous strains.[60] The use of native fermenters in plant substrates offers the following advantages[60,61]: (i) rapid acidification, (ii) high cell growth, (iii) safety, which is unlikely to contain harmful bacteria, (iv) more consistent and desirable flavor and texture in the final product produced, (v) high juice viscosity, (vi) high consumption of fermentable carbohydrates, (vii) more extended survival period, and (viii) lower cost.

Hence, GM would be suitable for lactic acid fermentation, while some pretreatment (ethanol soaking) or addition of exogenous cofactors (tanninase, phenolic acid reductase) might be needed to remove tannins and other partial phenolic compounds before fermentation to achieve favorable results. Moreover, the selection of the appropriate strain for fermentation is a priority.

Effect of polyphenols in grape marc on lactic acid bacteria

Despite their existence as a natural plant microbiota, lactic acid bacteria are still susceptible to phenolic compounds. In the context of lactic acid fermentation, polyphenols can inhibit the growth of lactic acid bacteria by several mechanisms. (i) Antimicrobial properties: polyphenols can directly inhibit the growth of LAB by interacting with their cell membrane and cell wall, leading to membrane permeabilization and leakage of essential intracellular components.[62] (ii) Chelation of metal ions: polyphenols chelate metal ions such as iron, zinc, and copper,[63] which are essential for the growth and metabolism of LAB. (iii) Inhibition of enzymes: polyphenols can inhibit the activity of enzymes such as catalase, superoxide dismutase, and glucose-6-phosphate dehydrogenase,[64,65] which are essential for the growth and metabolism of LAB.[66] (iv) Competition for nutrients: polyphenols compete with LAB for essential nutrients through their interaction, such as sugars, amino acids, and vitamins,[67] which could limit LAB growth.[68]

The inhibitory effect of polyphenols on lactic acid bacteria is also contingent on the concentration[69] and the specific strain used. *L. plantarum*, which has demonstrated considerable metabolic activity against phenolic compounds,[13] is one of the most commonly utilized species for plant substrate

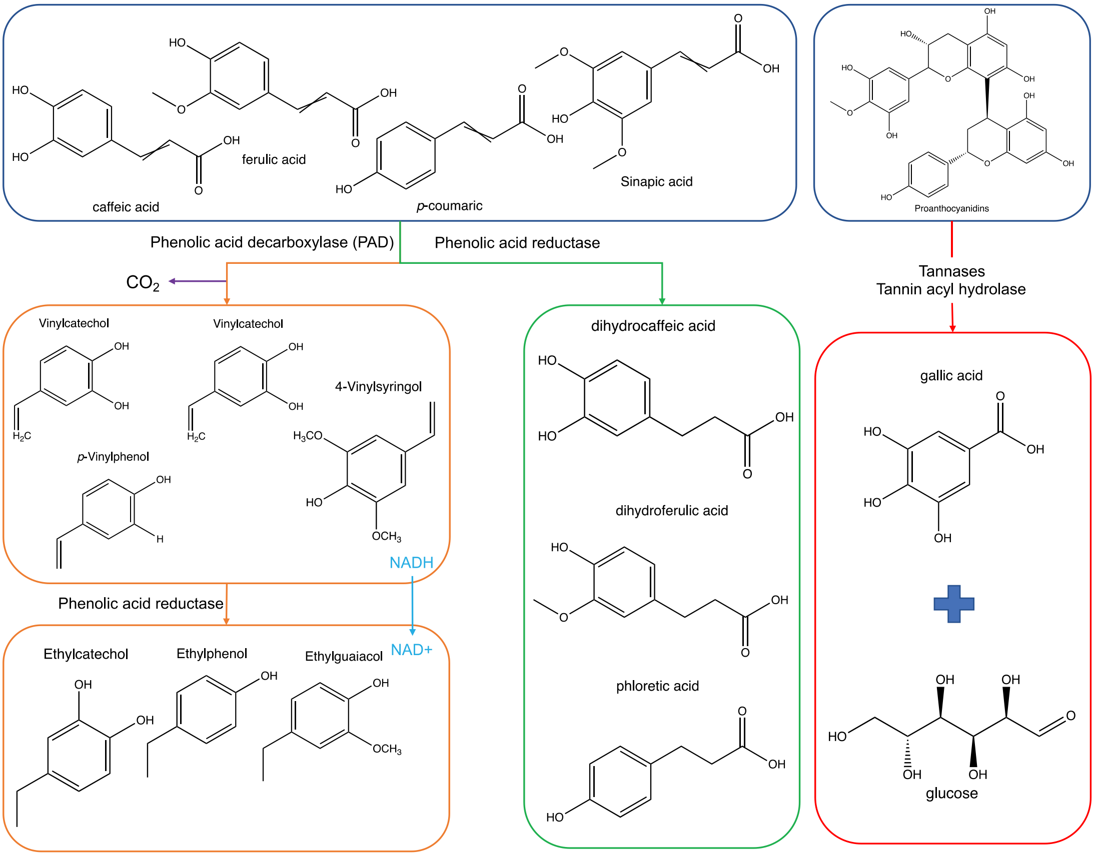


Figure 2. Phenolic compound metabolism by lactic acid bacteria.

fermentation. It is pertinent to note that not all polyphenols exhibit the same inhibitory effect on lactic acid bacteria, and in some instances, they can even promote the growth of specific strains. Notably, *p*-coumaric and ferulic acid have been shown to have the most substantial inhibitory effects on *L. plantarum*.[70] Conversely, caffeic acid and ferulic acid have been observed to stimulate the growth of *Lentilactobacillus hilgardii*.[71] Furthermore, catechins and epicatechin had no apparent inhibitory effect on *Lentilactobacillus hilgardii*.[72]

In the adaptation of plant-associated lactic acid bacteria, several enzymes are dramatically able to degrade polyphenols into less toxic derivatives, in particular, *β*-glucosidase, tannase, phenolic acid reductase, and decarboxylase.[13] The LAB degrades and modifies these secondary metabolites during the fermentation process (Fig. 2).

Tannases belong to the esterase superfamily and hydrolyze plant cell walls to release phenolic compounds bound to the cellulose matrix.[73] It is commonly used in the industry to clarify wines and juices. The degradation of tannins by *L. plantarum* has been shown to be as high as 95%.[74] Reductases and decarboxylases primarily interact with several phenolic acids, resulting in vinyl derivatives; secondly, ethyl phenols will be produced by the action of a reductase enzyme.[75] Several LAB species are able to metabolize these substances by the action of enzymes. For instance, *Limosilactobacillus fermentum* is unable to metabolize hydroxycinnamic acids, whereas it could convert them into vinyl derivatives by decarboxylation.[76] On the other hand, *β*-glucosidase can effectively hydrolyze the glycosidic bonds in glucosides, thereby releasing carbohydrates which can be further utilized as energy.[13] This enzyme has been detected in various strains of *L. plantarum*, *L. fermentum*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii subsp. bulgaricus, Lacticaseibacillus casei*, and *Bifidobacterium sp.*.[77,78]

Table 2. Comparison of chemical and nutritional characteristics in grape marc with added 1% glucose (GMG): GMG un-inoculated vs. inoculated with selected bacterial Strains.[56].

	GMG un-inocluated	*L. plantarum* 12A	*L. plantarum* PU1	*L. paracasei* 14A	*B. breve* 15A
pH	5.32	3.62	3.76	3.65	3.63
Total titratable acidity (g/L)	1.24	4.51	6.19	5.85	6.24
Carbohydrates (g/L)	9.51	1.22	-	-	-
Lactic acid (g/L)	0.00	2.88	4.73	3.85	4.60
Citric acid (g/L)	0.45	0.18	0.12	0.20	0.09
Minerals (mg/Kg)					
Phosphorus (P)	359	328	286	221	348
Calcium (Ca)	200	149	159	232	171
Potassium (K)	2361	2186	2148	1922	1927
Magnesium (Mg)	80	91	77	63	72
Sodium (Na)	916	1058	1046	1039	1062
Fiber (%)					
Insoluble fiber	0.07	0.36	2.15	0.63	0.85
Soluble fiber	0.60	0.80	0.80	0.70	0.80
Vitamins (mg/Kg)					
Vitamin B1	0.18	0.14	0.10	0.17	0.10
Vitamin PP	10.30	10.90	10.10	10.10	9.80
Free amino acids (mg/kg)					
Total	3051.30	2018.25	2092.66	2029.95	2068.41
Tryptophan	40.91	49.33	46.17	52.62	46.75
Phenolic compounds (mg/L)					
Total phenol content (Gallic acid equivalents per liter)	1123	1028	932	1000	977
Gallic acid	68.00	12.60	10.10	10.80	9.40
(+)-Catechin	3.50	3.40	3.20	3.20	3.30
(−)-Epicatechin	71.40	61.70	55.50	55.20	54.30
Procyanidin B1	14.90	10.50	13.50	10.90	14.60

[a]– means not detected.

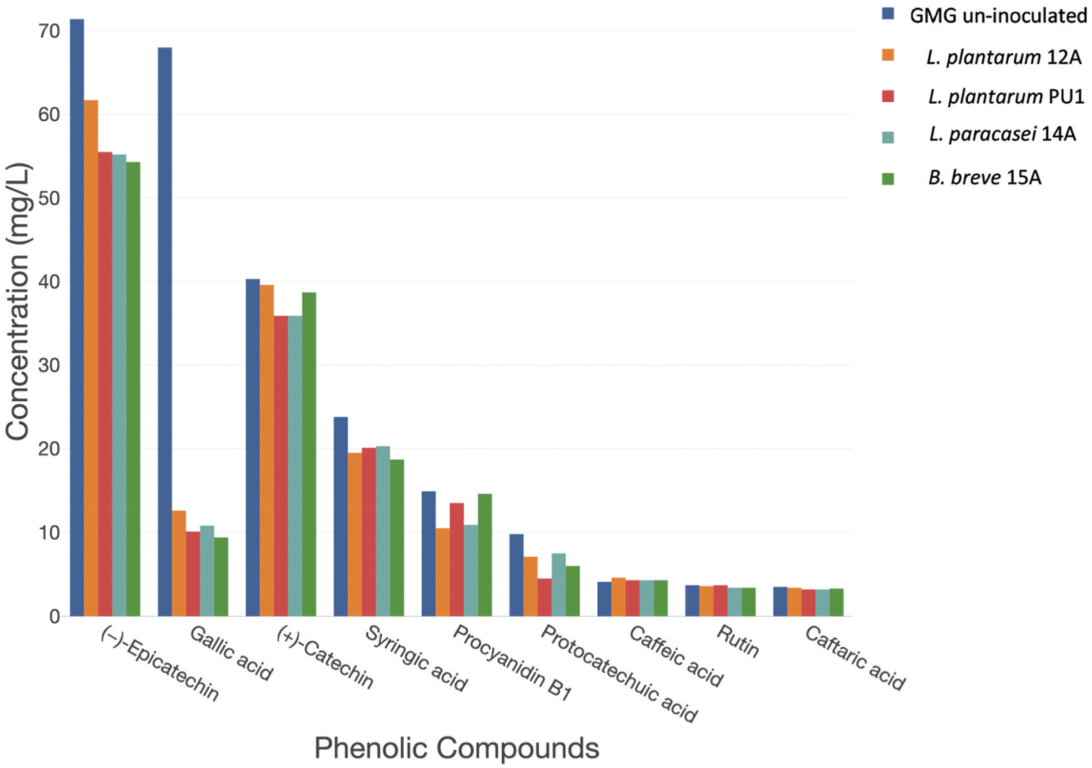


Figure 3. Alterations in polyphenol content of grape marc with added 1% glucose: A comparison between GMG un-inoculated and inoculated with selected bacterial strains. The figure was prepared from data retrieved from.[56].

Major changes in the composition and bioactivity of fermented grape marc

As lactic fermentation proceeded, several compositional changes can be observed in the GM. The biotransformation of phenolic compounds is is highly influenced by the strain used, and any changes in the phenolic content during fermentation are attributed to various factors such as substrate, pH, temperature, and fermentation duration. According to Daniela et al.,[56] the total phenolic content of GM was observed to remain relatively unchanged after undergoing fermentation with different strains of LAB (as illustrated in Table 2). There was an obvious loss of gallic acid after fermentation, while the loss of other phenolic compounds was not significant (Figure 3). The *in vitro* antioxidant activity of GM fermented by LAB and bifidobacteria strains did not change significantly. However, it is noteworthy that GM fermented by *L. plantarum* PU1 revealed a remarkably antioxidant capacity close to that of α-tocopherol and butylated hydroxytoluene.[56] In the study conducted by Jose´ Mari ´A Landete et al., the significant reduction described above in the concentration of gallic acid was found to be in congruence with the discerned metabolic activity of both gallic acid and methyl gallate by *L. plantarum* strains.[79] These strains exhibit the capacity to catalyze the hydrolysis of ester linkages present in tannins, such as tannic acid, leading to the liberation of glucose and gallic acid. Following this, the gallic acid undergoes a decarboxylation reaction, culminating in the formation of pyrogallol. This compound, characterized by the presence of three contiguous hydroxyl groups, is a potent antioxidant and is recognized as the most efficacious scavenger of free radicals among simple phenolic compounds. This phenomenon could elucidate the noteworthy diminution in gallic acid content, while concurrently accounting for the augmentation in total antioxidant capacity.[79]

Various studies have investigated the use of fruit substrates for lactic fermentation, with some reports indicating a significant increase in antioxidant capacity post-fermentation. For instance, tannase-mediated degradation of ellagitannins from pomegranate during lactic fermentation[80] led to the formation of simpler phenolic forms such as ellagic, gallic, ferulic, caffeic, and quinic acids, which have potent antioxidant potential.[81] However, it has also been observed that the conversion and depolymerization of high-molecular-weight phenols to simple phenolic forms significantly reduces the total phenolics and flavonoids in fermented apple juice.[82] Fermentation-induced metabolization of quinic acid, quercetin-3-*O*-galactoside, quercetin-3-*O*-glucoside, and phlorizin into 5-*O*-caffeoylquinic acid, quercetin, and phloretin was also noted, with the end products exhibiting enhanced antioxidant activity compared to their precursors.[82] Although the mechanism of phenolic degradation during plant fermentation is not fully clarified, LAB still successfully produces bioactive compounds of human interest.

Lactic acid is the main metabolite produced by LAB. *L. plantarum* PU1 produced the highest amount of lactic acid after fermentation.[56] During the production of lactic acid, LAB consumes sugars, such as glucose and fructose, which leads to a decrease in their concentration. Significant catabolism of free amino acids in all fermented samples suggests that they were used as alternative carbon sources by selected LAB.[56] Plenty of LAB are able to utilize citrate as an electron acceptor to co-metabolize with glucose, fructose, lactose, or xylose, providing NADH for pyruvate reduction[83] (shown as Figure 4). In the presence of glucose and citrate, each mole of citrate produces one mole of pyruvate without the need for NADH, resulting in excess intracellular pyruvate. Pyruvate is then channeled into the synthesis of α-acetolactate, giving rise to the production of C_4 aromatic compounds. The final products of this co-metabolism are lactate, diacetyl, and acetoin, as well as γ-butanediol.[84] Overall, the ability of LAB to efficiently transport and metabolize carbohydrates and other carbon sources (such as citric acid and free amino acids) is critical for maintaining growth and persistence under non-optimal or stressful conditions, such as low pH condition.

Lactic acid fermentation can also yield other metabolites, such as ethanol, acetic acid, and carbon dioxide, albeit in small amounts that are contingent on the fermentation conditions and the specific

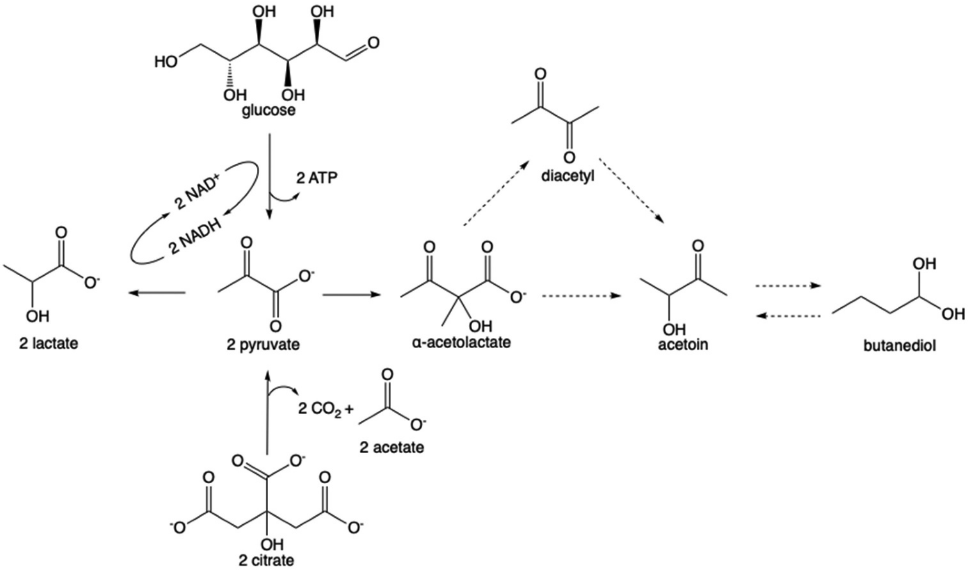


Figure 4. Co-metabolism of citrate and glucose in autochthonous lactic acid bacteria.

LAB employed. As lactic acid and other acidic substances are produced, the pH of the system would decrease correspondingly.

It was observed that LAB and bifidobacteria strains cultivated on GM exhibit tolerance under simulated gastrointestinal conditions, indicating that these probiotics can withstand the harsh effects of gastric juices during their transit through the gastrointestinal tract. Following this, the impact of fermented GM on Caco-2 cells was assessed for cytotoxicity, with significant increases in antioxidant activity found after fermentation.[56] Furthermore, distinct variations in survival and potential probiotic effects were noted among *L. plantarum* strains. Insights from genomic studies have indicated that the presence or absence of various DNA regions in different strains of *L. plantarum*, including areas responsible for bacteriocin production, exopolysaccharide synthesis, and sugar metabolism, may influence the adaptability and viability of the organisms in diverse ecological niches, ultimately affecting their potential as probiotics.[56]

Formation of flavor compounds in fermented grape marc

Flavor constitutes the amalgamation of gustatory and olfactory experiences triggered by a substance within the oral cavity, and its assessment is achieved through sensory analysis. This sensory experience is engendered from (1) a subset of water-soluble taste compounds that pertain to the quintessential tastes of sweetness, saltiness, bitterness, sourness, and umami; and (2) a multitude of aroma compounds, which are volatile odoriferous substances, and they account for the diversified flavor profiles distinctive to fermented foods.[85]

The aroma profile and flavor of fruit substrates are enhanced through lactic acid fermentation, as displayed in Table 3. According to their chemical composition, aroma components in fruit substrates can be categorized into volatile, non-volatile, and acidic groups. Volatile compounds encompass alcohols, acids, ketones, hydrocarbons, aldehydes, and esters. Non-volatile compounds primarily consist of amino acids, including L-serine, L-proline, L-glutamic acid, and L-aspartic acid. The acidic group comprises citric acid, malic acid, and lactic acid.[13]

Diacetyl is one of the primary aromas produced by citrate in lactic fermented grape matrices.[95] At low concentrations (1–4 mg/L), diacetyl produces a typical butter-like character, while at high concentrations (>5–7 g/L), it gives undesirable aromas.[96] Glycosidases in LAB release aromatic substances through the cleavage of glycoside molecules and volatile aromatic glycoside ligands, for instance, terpenes, C_{13} norisoprenoids, volatile phenols, and C_6 compounds.[97] Conversely, the activity of glycosidase may adversely influence the quality of the end product. Similar to yeast, LAB possess the ability to decompose sugar complexes, which can significantly impact the evolution of volatile phenolics related to smoke flavors. This effect, in turn, modifies the intensity of aromas associated with smoke.[98] Aroma compounds related to smoky and earthy flavors[99] (e.g., guaiacol, 4-methylguaiacol, 4-ethylguaiacol, and 4-ethylphenol) could be released by enzymatic hydrolysis of conjugated precursor compounds.[100]

Ethyl phenols are vital aromatic compounds involved in unpleasant odors in grape products, like horse sweat, leather, and stable. The LAB is directly responsible for producing 4-vinylphenol,[101] and studies have shown that the presence of hydroxycinnamic acid (especially caffeic acid) enhances this activity, yet tannins at around 1 g/L inhibit the release of volatile phenolics by LAB.[101] However, it has also been suggested that the intermediate vinylphenols could react with anthocyanins to produce stable vinylphenolic pyranoanthocyanins.[102] The presence of vinylphenols in this bound form may help to reduce the amount of precursors forming ethyl phenols and stabilize the color of the final product.[103]

Acetaldehyde, a crucial compound found in grape products, significantly influences numerous aspects, including aroma, color, stability, and microbiological properties. When present in low concentrations, acetaldehyde serves to accentuate the fruity essence of the given product. However, a surge in its concentration results in the production of a distasteful odor reminiscent of rotten

Table 3. Formation of flavor substances common when LAB ferment fruits or their by-products.

Type	Compound	Degradation	Flavor compounds produced by LAB	Sensory evaluation	Reference
Amino acids	Leucine, Isoleucine, Valine (Branched-chain Amino Acids)	These amino acids were degraded by all strains of LAB. The volatiles detected in ripened cheese originated mainly from leucine and valine. The degradation of free amino acids by each strain was dependent on pH, with an optimum pH of around 6.0.	Isovaleric acid, 2-methylbutanoic acid, isobutyric acid	Malty, fruity, and sweaty flavors	[86,87]
	Phenylalanine, Tyrosine, Tryptophan (Aromatic Amino Acids)	Transamination requires α-keto acids as co-substrates. Glutamate dehydrogenase activity is the main criterion for the selection of aromatic compounds producing LAB strains.	Phenethyl alcohol, phenethylamine, tyramine, and tryptamine	Floral and honey-like, chemical flavors	[85,86]
	Aspartic Acid	First, aspartic acid is converted into oxaloacetic acid by the enzyme aspartate transaminase. Oxaloacetic acid is then converted into pyruvic acid by the enzyme malate dehydrogenase. Pyruvic acid is then converted into acetaldehyde by the enzyme pyruvate decarboxylase.	Carboxylate esters	Buttery flavors	[88,89]
	Methionine, Cysteine (Sulfuric Amino Acids)	LAB ferments sulfuric amino acids like methionine and cysteine to produce volatile sulfur compounds. While nearly all strains of these bacteria produce volatile sulfur compounds from methionine, the exact enzyme responsible for this activity is not clear.	Methanethiol, dimethyl disulfide, dimethyl trisulfide, and hydrogen sulfide	Boiled cabbage, meaty, and garlic flavors	[85,86,90]
Carbohydrates	Glucose, fructose	Homofermentative pathways generate lactic acid as the main end-product, whereas heterofermentative metabolism results in some other metabolites. Under specific circumstances such as limited carbon availability, excess of slowly metabolised sugars, or aerobic conditions, a transition can occur from a predominantly homofermentative metabolism to a mixed-acid metabolism, characterized by a diverse array of metabolites.	Lactic acid, ethanol, carbon dioxide, acetic acid, acetaldehyde, diacetyl, acetoin, and 2,3-butanediol	Green apple, nutty or buttery flavors	[89]
Organic acids	Malic acid	Decarboxylation. During which the malic acid (a dicarboxylic acid) is transformed into lactic acid (a monocarboxylic acid). This change leads to a decrease in the wine's overall acidity and the creation of a smoother, rounder mouthfeel.	Diacetyl, esters, higher alcohols, acetic acid, ethyl acetate, sulfur compounds	Buttery, butterscotch, fruity and floral flavors	[91,92]
	Citric acid	LAB, particularly species from the genera *Oenococcus*, *Lactobacillus*, and *Pediococcus*, can metabolize citric acid present in grape must during the winemaking process. The citric acid metabolism proceeds through a series of biochemical reactions known as the "citric acid cycle" or "tricarboxylic acid cycle."	Diacetyl, carbon dioxide, acetoin, 2,3-Butanediol	Buttery, butterscotch, mild, sweet, and creamy flavors	[83,93]
	Tartaric acid, quinic acid	These acids can also be served like citric acid as carbon sources for some LAB strains.	Diacetyl, carbon dioxide	Buttery and butterscotch flavors	[93,94]

apples.[103] Autochthonous and allochthonous lactic acid bacteria (LAB) strains have been documented to possess the capability to decompose free acetaldehyde and sulphur dioxide-bound acetaldehyde. The degradation process results in the formation of minimal quantities of ethanol and acetic acid. Nevertheless, this could inadvertently lead to a notable elevation in the volatile acidity levels of the final product, an undesirable outcome.[104]

Improvement strategy of fermented grape marc as a functional food

With increased attention to diet, the functionality and health benefits of foods are becoming increasingly important. Fermented foods stand out because of their improved organoleptic properties, rich health benefits, easier absorption, and cost-effectiveness. As described above, GM is indeed a reasonable product suitable for lactic acid fermentation, but several improvements are needed to promote it as a product widely accepted by the public.

Food safety is always a priority. During the fermentation process, some harmful substances are produced.[105] Pathogenic microorganisms could cause human diseases. Mycotoxins are toxic compounds produced by certain types of molds. They are all present in the raw material and grow during the fermentation process. If left uncontrolled, they could contaminate the final product and pose a risk to human health. Acetic acid, ethanol, and hydrogen sulfide are by-products of the fermentation process and lead to the deterioration of the fermentation product.[106] Acetic acid causes changes in acidity in the final product, and high ethanol levels may also harm human health. Hydrogen sulfide produces an unpleasant odor and taste.

Lactic acid bacteria and other microorganisms produce biogenic amines through the decarboxylation of amino acids,[107,108] which are potentially dangerous compounds that can cause adverse health effects such as headaches, nausea, and high blood pressure. Ethyl carbamate is found in many fermented foods and beverages and is a carcinogenic compound.[107] The reaction of ethanol with N-carbamoyl compounds is the main reason for the formation of ethyl carbamate in grape products.[109] Another problem that could occur during fermentation is the contamination of lactic acid fermenters with phage.

These problems can be overcome by controlling the fermentation process with constant monitoring of pH, organic acids, and volatile compounds formation; by the screening of novel lactic acid fermentation strains and addition of exogenous co-fermentation factors; or even by genome editing to give lactic acid bacteria greater environmental adaptability or more functions.[92]

One of the research directions is finding a better way to include more functions and health benefits in the final product. It is possible to transform the rich natural antioxidant sources in GM into more bioavailable small molecules that can provide superior antioxidant capacity, longer shelf life, richer taste, and even some therapeutic effects for clinical diseases in the final product. Improved fermentation processes could be integrated with nanotechnology, for example, the inclusion of nutrients in controlled release systems as nanoparticles leads to better results, including controlled release and enhanced efficacy, like in the treatment of diabetes,[110] and even in the formulation of prebiotics, probiotics, and commensal bacteria.[111]

The survival of cells during storage is an essential issue that must also be considered. For functional foods, it is necessary to maintain high cell viability during the resting growth period in the substrate environment. In this regard, microcapsules could protect cells from refrigeration conditions and digestion.[112]

These issues discussed above can be overcome by constantly monitoring pH, organic acid, and volatile compound formation to control the fermentation process; by screening novel lactic acid fermentation strains[92] and adding exogenous co-fermentation factors; or even by genome editing to give lactic acid bacteria greater environmental adaptability or more functionality, such as by cultivating strains that express phenolic compound degrading enzymes.[113]

Simultaneously, more efficient and cost-effective fermentation methods are needed to produce functional compounds from GM. With the advances in biotechnology, solid-state fermentation,[114] submerged fermentation,[115] and continuous fermentation[116] are emerging as innovative fermentation processes that could improve the yield and quality of functional compounds from GM and reduce the cost of fermentation.

Conclusions

The fermentation of GM with LAB is a promising approach for valorizing and producing functional food and beverage ingredients. The fermentation process converts the sugars and amino acids present in GM into lactic acid, improving the final product's preservation and organoleptic properties. Additionally, lactic acid fermentation increases the concentration of antioxidants, vitamins and minerals, and other functional compounds in GM.

However, there are still some limitations and areas of improvement that need to be addressed in future research. Developing more efficient and cost-effective fermentation processes, such as solid-state fermentation, submerged fermentation, and continuous fermentation, could improve the yield and quality of functional compounds from GM. Autochthonous starter cultures are known to play an essential role in the fermentation process and contribute to the final product's flavor, aroma, and stability, whereas more research is needed to identify and optimize the use of these starter cultures to produce functional compounds from GM. In addition, the effects of different processing methods, including drying, milling, and pressing, on the composition and bioactivity of GM need to be studied further.

The sustainable use of GM is an essential area of interest, as it can reduce the environmental impact of winemaking and increase the economic value of GM. The development of novel methods for the valorization of GM and its use in the production of functional foods and beverages could contribute to the sustainability of winemaking. It will also provide the public with new consumption options.

Disclosure statement

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