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Microbiota for production of wine with enhanced functional components

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ABSTRACT

Microbial communities during winemaking are diverse and change throughout the fermentation process. Microorganisms not only drive alcohol fermentation, flavor and aroma, but also enhance wine functional components such as extraction of polyphenols from the berries, production of γ-aminobutyric acid, hydroxytyrosol and melatonin. Polyphenols such as resveratrol, catechin and quercetin determine the functional quality of the wine. Moderate wine consumption, particularly red wine has been associated with functional benefits to human health, which includes anti-inflammation, promoting healthy aging, prevention of cardiovascular diseases, cancers, type 2 diabetes and metabolic syndrome. Indeed, the management of microbiota allows the production of wine with distinct features and functional components that benefits human health. This review scrutinizes the possible contributions of wine microbiota to the production of wine with enhanced functional components and highlights the contributions of *Saccharomyces* and non-*Saccharomyces* yeasts and bacteria to enhance wine functional components during winemaking. Thus, contributing to the dissemination of the benefits of light to moderate wine intake to human health.

1. Introduction

Fermentation of grapes must to make wine is a complex biotechnological process, which involves the cooperative actions of yeast and lactic acid bacteria (LAB). Traditionally, studies on the wine microbial interactions have mostly focused on the two key fermentation processes: alcoholic fermentation by *Saccharomyces cerevisiae* and malolactic fermentation by *Oenococcus oeni* [1,2]. The contributions of yeast and bacteria to wine fermentation and the technology chosen are crucial factors, which influence the overall wine composition.

Mostly, wine fermentation is dominated by *S. cerevisiae*. However, some non-*Saccharomyces* yeasts and bacteria actively take part to develop characteristics of a unique wine profile. For instance, yeasts of the genera *Brettanomyces*, *Candida*, *Cryptococcus*, *Debaryomyces*, *Hanseniaspora*, *Hansenula*, *Klyveromyces*, *Pichia*, *Rhodotorula*, *Saccharomyces*, *Schizosaccharomyces*, *Sporidiobolus*, *Torulaspora*, *Zygoascus* and *Zyogosaccharomyces* have been isolated from grapes and fermenting must [3-5]. Also, bacteria of the genera *Lactobacillus*, *Leuconostoc*, *Oenococcus* and *Pediococcus* have been reported to take part in malolactic fermentation and wine maturation [6]. Malolactic fermentation is the biological transformation of malic acid to lactic acid, which increases wine pH and impacts microbial and flavor stability. On the other hand, fungi genera of *Alternaria*, *Aspergillus*, *Botrytis*, *Cladosporium*, *Oidium*, *Penicillium*, *Plamapara* and *Rhizopus* have been reported to infect and colonize the grapes [7,8]. Species of *Aspergillus*, *Botrytis*

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and *Penicillium* produce metabolites that modify the environment for yeast and LAB growth during fermentation. For instance, noble wine, which is produced from noble rot grapes infected by *Botrytis cinerea* shows a unique flavor, high polyphenols and sugar content [9,10]. Indeed, spontaneous wine fermentation can be caused by a complex community of microorganisms naturally present on the grape as well as the harvest and winery equipment. As a result, controlled fermentation with selected commercial *Saccharomyces* and non-*Saccharomyces* yeasts has attracted attention in the wine industry and research in an effort to enhance wine functional components and efficient alcohol production. However, winemakers use a different strategy to inhibit unwanted microorganisms, such as the addition of sulfur dioxide (SO_2), sterilization or clarification to design and produce various wine specialties.

Wine benefits to human health are contributed by its complex matrix of compounds: polyphenols, organic acids, tannins, minerals, proteins and microbial metabolites. Among these compounds, dietary polyphenols and microbiota metabolites show anti-inflammatory, anti-bacterial, anti-fungal, anti-proliferative and anti-hypertensive activity. So, ancient Greeks, Romans and Egyptians took wine as medicine to treat wound injury, gastrointestinal and urinary tract diseases, or used it as the delivery vehicle for other medications [11,12]. Today, wine is an important beverage having health benefits such as the prevention of cardiovascular diseases, which are linked to moderate wine consumption.

Wine polyphenols include phenolic acids, flavonoids, flavonols, anthocyanins, proanthocyanins and stilbenes (resveratrol). The antioxidant effect of wine as contributed by polyphenols has been demonstrated in several studies, from *in vitro* to *in vivo* investigation in human subjects. In addition to antioxidant activity, red wine polyphenols were shown to possess many functional properties including the inhibition of platelets aggregation, vasorelaxation activity, reducing the risks of heart disease, modulation of lipid metabolism, inhibition of low-density lipoprotein (LDL) oxidation, anticarcinogens, modulation of the gut microbiota and protecting the cognitive function in humans [13,14]. Therefore, this review aims to explore the application of wine microbiota to produce wine with enhanced functional components in terms of polyphenols and microbial metabolites.

2. Yeast diversity in the wine microenvironment

During winemaking, grape must undergo a sequential transformation in which populations of yeast species lead to different qualities of wine. These yeasts can provide characteristics of the grape growing region, flavor, aroma, alcohol levels, acidity and color of the wine. Although the entire wine microbial community contributes to wine composition, yeasts play a predominant role in alcohol fermentation [15]. However, some yeast species like *Pichia manshurica* release compounds, which impact wine with off-flavors and odors [16].

Some of the non-*Saccharomyces* yeasts predominate the initial stages of fermentation until *S. cerevisiae* function when ethanol concentration increases [17,18]. Fermentation often begins with the proliferation of weak fermentative non-*Saccharomyces* yeasts of *Candida*, *Debaryomyces*, *Hanseniaspora*, *Metschnikowia* and *Pichia*. These yeasts cannot tolerate the increasing alcohol concentration as well as depleted oxygen and nutrients, and are thus killed [19,20]. The strong fermentative species of *Torulaspora delbrueckii* and *Lachancea thermotolerans* proliferate until oxygen depletes, and thus *S. cerevisiae* [18]. Consequently, *S. cerevisiae* is routinely used as a commercial starter culture for alcohol fermentation, to produce desirable wine metabolites. However, the use of pure *S. cerevisiae* cultures could lead to the production of wine with standardized characteristics and therefore the use of mixed culture fermentation with non-*Saccharomyces* and *Saccharomyces* was proposed to produce wines similar to spontaneous without the risk of sluggish or stuck fermentations. Consequently, the use of non-*Saccharomyces* was further encouraged in recent years to produce wine with an increased level of specific metabolites.

Today, winemakers use indigenous non-*Saccharomyces* yeasts as part of wine production to incorporate various characteristics. However, the growth of some of the non-*Saccharomyces* yeasts may cause antagonistic interactions between yeasts and leads to the accumulation of metabolites, including acetic and lactic acids, glycerol, aldehydes, acetoin, acetate esters, higher alcohols and ethyl fatty acid esters [21]. Some non-*Saccharomyces* yeasts such as *Candida* spp., *Cryptococcus* spp., *Hanseniaspora* spp., *Hansenula* spp., *Metschnikowia* spp., *Pichia* spp., *Rhodotorula* spp. and *Zygosaccharomyces* have been shown to survive in wine fermentation at low-alcohol concentration. In addition, some yeasts are resistant to ethanol and survive during fermentation for a significantly long period. For instance, *Schizosaccharomyces pombe*, *T. delbrueckii*, *Starmerella bacillaris* and *Zygosaccharomyces bailii* can survive alcoholic fermentation for their resistance to ethanol [20]. Over 22 non-*Saccharomyces* yeasts, which have been shown to directly influence wine quality include *Aureobasidium pullulans*, *Brettanomyces bruxellensis*, *Candida inconspicua*, *Candida stellata*, *Candida vini*, *Cryptococcus magnus*, *Cyberlindnera jadinii*, *Hanseniaspora uvarum*, *Hanseniaspora apiculate*, *Metschnikowia pulcherrima*, *Pichia fermentans*, *Pichia kluyveri*, *P. manshurica*, *Pichia membranifaciens*, *Pichia occidentalis*, *Rhodotorula glutinis*, *Rhodotorula mucilaginosa*, *Saccharomycodes ludwigii*, *S. bacillaris*, *T. delbrueckii*, *Wickerhamomyces anomalus* and *Z. bailii* [22]. For this reason, strains of *L. thermotolerans*, *K. wickerhamii*, *Metschnikowia fructicola*, *M. pulcherrima*, *P. kluyveri*, *S. pombe*, *S. bacillaris* and *T. delbrueckii* are commercially used in winemaking [23,24]. Also, their enzymatic activities enhancing functional polyphenols have been assayed including β-glucosidases, proteases and pectinases.

The significance of β-glucosidases in winemaking is their potential on releasing flavor compounds from glycosidic bounded and non-volatile flavorless compounds in fermenting wines [25]. The β-glucosidases activity was reported in yeast genera of *Candida*, *Debaryomyces*, *Hanseniaspora*, *Hansenula* and *Pichia* [26]. Co-fermentation of must with *S. cerevisiae* and glucosidases active non-*Saccharomyces* yeasts of *Debaryomyces vanriji*, *Hanseniaspora* spp., *Issatchenkia terricola*, *Pichia anomala*, *Pichia kudriavzevii* and/or *Metschnikowia pulcherrima* produced a wine with increased terpenes and free resveratrol concentrations [27,28]. Terpenes such as linalool, nerol, citronellol, geraniol, α-terpineol and linalool oxide are components that contribute to wine flavor and aroma profile [29,30]. A study conducted by de Ovalle et al. [31], indicated that *I. terricola* β-glucosidases activity in red wine increased levels of phenolic guaiacol, 2,6-dimethoxyphenol and norisoprenoids volatile aroma.

Likewise, β-glucosidases of *Hanseniaspora uvarum* strains hydrolyze resveratrol-glucosides in wine. Other non-*Saccharomyces* yeasts with β-glucosidases activity are *Debaryomyces polymorphus*, *Debaryomyces castelli*, *Debaryomyces hansenii*, *Hansenula anomala* and *Hanseniaspora apiculate* [5].

The proteases are responsible for the degradation of grape and haze proteins, and aid in wine clarification. Non-*Saccharomyces* yeasts are an important source of proteases, and have been established to possess higher proteolytic activity than *Saccharomyces* yeast. Proteolytic activity in non-*Saccharomyces* yeasts may contribute to increased peptides, amino acids and assimilable nitrogen in the fermenting wine and facilitate the extraction of polyphenols from the grapes [32]. The peptides and amino acids from the proteolytic activity are oenologically important metabolites due to their role as nutrients for LAB during malolactic fermentation. For instance, the growth of *O. oeni*, a malolactic fermentation bacteria with probiotics potentials, depends on the presence of amino acids and assimilable nitrogen due to their deficiency of the synthetic pathway [33].

Pectinases are an assemblage of enzymes, each of which is involved in the depolymerization or hydrolysis of specific forms of pectin, which is a component of plant cell walls composed of methyl esterified galacturonic acid linked with α-(1-4)-glycosidic bonds [34]. Pectinases degrade polysaccharides, and thus increase the release of phenolics, color and aroma compounds contained in the berry skin during fermentation. The increase in pigments and polyphenol improves the functional properties of the wine. Moreover, pectinolytic enzymes improve wine liquefaction, clarification and filtration. However, most of the Saccharomyces yeasts do not show pectinolytic activity [33]. In contrast, non-*Saccharomyces* yeasts of *Klyuveromyces marxiamunus*, *M. pulcherrima*, *M. fructicola* and *R. mucilaginosa* produce pectinases [35,36].

3. Application of non-*Saccharomyces* yeast in wine industries

Non-*Saccharomyces* yeasts produce several compounds, which have a significant influence on ethanol reduction, control of spoilage microorganisms, polyphenols, flavor and aroma, thus improving functional properties and overall quality of the wine (Table 1). However, these yeasts typically need to be sequentially or co-inoculated with *S. cerevisiae*. For instance, the use of *S. cerevisiae* and non-*Saccharomyces* isolates *S. bacillaris* (STS12) and *H. uvarum* (STS45) taking advantage of spontaneous fermentation, enhanced the chemical and organoleptic characteristics of Montepulciano d'Abruzzo wine, a popular red grape wine in Italy [37].

Wine alcohol content ranges 9%–15% (*V/V*), with some exceptions that may be as low as 8.5% and as high as 20% (*V/V*) depending on climate, soil, vine variety, wine style and specialty processing [51]. Banrock station Bright Idea (Accolade), Lindemans Early Harvest (Treasury) and Jacob's Creek Cool Harvest (Pernod Ricard) with 5.5%, 7.5%–9% and 9.5%–11% alcohol, respectively are examples of low-alcohol wine brands in Australia [52]. In an extreme case alcohol concentration can be 4.5% (*V/V*) in wine, in Australia [53]. Low-alcohol wine is a new trend to deliver functional foods, for the increased health concerns, modern lifestyle and economic issues. Emerging production of wine with enhanced functional components and taxes imposed on alcohol concern a spike to reevaluate the potentials of wine microbiota. Long-term health implications associated with alcohol consumption have also contributed to the development of low-alcohol wine [39]. For instance, excessive consumption of alcohol has been linked to the digestive tract, liver and breast cancer and early death in most developed countries, and is a significant contributor to the global burden of disease. In addition, wine polyphenols such as resveratrol that even when they have interesting "*in vitro*" effects, the amount in wine and the plasmatic absorption may need several bottles per day to have a health protective effect. In such conditions wine alcohol may be a problem and need a strategy to reduce alcohol in wine.

Alcohol reduction in wine is to reduce alcohol-related harms without compromising the functional components and beneficial aspects of moderate consumption [54]. As the consequence, some winemakers have developed de-alcoholization techniques to come up with low-alcohol wine. Wine de-alcoholization can be achieved through 1) viticulture method of vineyard management, 2) pre-fermentation method by dilution of must, membrane-based technologies such as reverse osmosis, nanofiltration and use of enzymes or microbes, and 3) post-fermentation method (vacuum distillation, spinning cone column, membrane methods or solvent supercritical extraction and pervaporation) [51]. However, de-alcoholization is not always a proper choice, since some wine components might be compromised and the bioavailability of beneficial factors may be altered in the absence of ethanol. For the

Table 1
Application of some non-Saccharomyces yeast in wine industries.

Non-*Saccharomyces* yeast	Function in wine	References
H. uvarum, *I. terricola*, *L. thermotolerans*, *M. pulcherrima*, *P. kluyveri*, *S. ludwigii*, *S. bacillaris*, *T. delbrueckii*, *Z. bailii*	Production of low alcohol wine and enhances aroma profile	[38-40]
L. thermotolerans	Modulates wine pH and reduces volatile acid flavor	[41]
S. bacillaris	Enhances wine quality, sensory perception and body structure like the spontaneously fermented wine	[42]
T. delbrueckii, *W. anomalus*, *M. pulcherrima*	Biocontrol activity against wine spoilage yeasts, thus sulfite reduction	[43-46]
Hanseniaspora spp., *P. kluyveri, T. delbrueckii*	Produces aroma compounds such as ethyl esters, which enhances wine flavor and improve wine organoleptic properties	[47]
M. pulcherrima	Enhance the polyphenol profile of wine in terms of anthocyanins and flavonoids, and give the wine a better color characteristic	[47,48]
S. pombe	Regulates wine acidity through malo-alcohol fermentation and help to shorten or eliminate the malolactic fermentation stage Used to produce wine higher in esters and low in acetic acid Reduce chances of ethyl carbamate and biogenic amines formation in wine	[49,50]

purpose of this review, only a microbiological approach using non-*Saccharomyces* yeasts will be presented.

A mixed culture of non-*Saccharomyces* and *S. cerevisiae* yeasts present a synergistic effect to produce low-alcohol wine [55]. They consume sugar at a slow rate of fermentation, producing moderate alcohol, hence prolonged fermentation time [56]. For instance, yeasts *H. uvarum*, *I. terricola*, *L. thermotolerans*, *M. pulcherrima*, *P. kluyveri*, *S. ludwigii*, *S. bacillaris*, *T. delbrueckii* and *Z. bailii* involved in the first stage of fermentation were shown to produce wine with 0.9%–2% less alcohol [39,57]. Varela et al. [55] reported a reduction of 1.6%–1.8% total alcohol of wine following co-inoculation with *M. pulcherrima*, *Saccharomyces uvarum* and *S. cerevisiae*. Similar findings were reported by Canonico et al. [40], using *T. delbrueckii*, *M. pulcherrima* and *Z. bailii* in the sequential fermentation with *S. cerevisiae*. Also, inoculating the must with *S. bacillaris* followed by *S. cerevisiae* after 48 h from the start of fermentation was proposed to reduce ethanol levels in wine [38]. Overall, while the use of non-Saccharomyces yeasts to produce low-alcohol wine is on the rise, improvement of the wine's functional characteristics has been occurring concurrently.

4. Bacteria in wine fermentation

Low pH in must and wine, high concentration of sugar and the presence of alcohol provide an environment for survival of limited microorganisms to just a few yeasts and bacteria. In winemaking, bacteria mostly LAB were linked to wine spoilage as lactic taint and tartaric acid. They are present throughout all stages of winemaking and can improve or diminish wine quality. They are involved in malolactic fermentation, and affect the organoleptic properties of the final wine product. LAB found in wine include the genera *Lactobacillus*, *Leuconostoc*, *Oenococcus* and *Pediococcus* [58-61]. Among these bacteria, *O. oeni* performs malolactic fermentation and grows in harsh oenological conditions: acidic pH, low nutrients and about 15% ethanol [62]. Therefore, if alcoholic fermentation by yeasts (*S. cerevisiae*) occurred, bacteria will show controlled growth. However, if alcoholic fermentation delays, various lactic and acetic acid bacteria may grow and inhibit yeast growth resulting in sluggish or stuck fermentation. Generally, winemakers can control the activity of bacteria and utilize their impact on the quality of wine to have balanced wine pH and desirable acidity. Whereas, acidity is an important factor of winery management for the determination of the wine pH, polyphenols, outset of malolactic fermentation as well as microbiological and organoleptic stability.

Malic acid imparts harsh acid mouthfeel, and in high concentration reduces wine quality [63,64]. Malolactic fermentation is an important process to reduce wine acidity and maintain the microbiological stability of the final product. It occurs spontaneously or by inoculation of commercial strains of LAB, usually *O. oeni* [2,65]. Additionally, strains of the genera *Lactobacillus* and *Pediococcus* can also induce malolactic fermentation. Malolactic fermentation is the enzymatic reaction in which *L*-malic acid, a dicarboxylic acid is converted to *L*-lactic acid, a monocarboxylic acid. The process increases the wine pH, reduces sourness, improves microbiological stability and results in enhanced aroma and flavor complexity [65,66]. The malolactic fermentation starts about 1–3 weeks after completion of alcoholic fermentation and last 2–12 weeks, depending on the environment, wine composition and amount of malic acid to be transformed [62].

When malic acid is completely converted, *O. oeni* disappears and LAB growth is inhibited, thus microbial stability. Nevertheless, opportunistic *Pediococcus* and *Lactobacillus* can be eliminated by the addition of sulfite once malolactic fermentation is completed. On the other hand, some yeast strains such as *S. pombe* have been shown to hydrolyze malic acid in the must and can shorten or eliminate the malolactic fermentation stage [50]. Additionally, *O. oeni* were reported to have β-glucosidases and esterase activities during malolactic fermentation [67]. For instance, *O. oeni* β-glucosidase activity facilitates the release of sugar from anthocyanin and quercetin glucosides for their growth during malolactic fermentation [68]. Thus, malolactic fermentation alters wine composition and the complexity of aroma and flavor. On the other hand, LAB associated with malolactic fermentation can have direct functional benefits to human health. For instance, the probiotic potential and immunomodulatory functions of *O. oeni* have been reviewed [69].

5. *B. cinerea* and botrytized wine

Botrytized wines are wine specifically made from overripe noble rotten grape, heavily infected by *B. cinerea*, withered and shriveled grapes [9,70]. Due to the particular characteristics of the noble rot, botrytized wine has distinct features, including a unique honey-like taste, fruity aroma and higher or lower residual sugar content [10].

B. cinerea can attack any part of the plant, although noble rot does not appear before grape maturity. The vascular disconnection between the berry and vine of fully matured or overripened grape indicates an appropriate time for *Botrytis* invasion to develop noble rot [71]. The fungal proliferation is promoted by high humidity at the night, foggy morning and dry-sunny days [72]. As *B. cinerea* hyphae grow into the grape berry, the grape skin cracks and water evaporates leading to dehydration of the berry resulting in shriveling of the berry and several-fold concentrations of the juice, an increase in sugar content, and a change in sugar and acid profile [70]. The perforated skin makes the grape accessible to several other microorganisms. As a result, noble rotten grapes are rich in microorganisms, including mold, yeast and bacteria [73,74]. The invaded microorganisms reduce some nutrients and produce metabolites that benefit or adversely affect must composition. Besides, noble rot can occur after harvest through spontaneous spoilage or upon inoculation with *B. cinerea* during postharvest withering of grapes [72].

B. cinerea produces several oxidases and hydrolases involved in the transformation of grape tissue and juice components. Several transformations happen simultaneously impacting fermentation performance and the organoleptic quality of wine, leading to different contents of sugar, organic acids and nitrogen-containing compounds [71]. The mold preferably metabolizes glucose, resulting in must with high fructose/glucose ratio that adversely impacts

yeasts growth and fermentation [75]. High sugar and sugar alcohol (glycerol, mannitol, sorbitol, arabitol and inositol) in the botrytized must constrains yeast activity, fermentation performance and a natural sweet noble wine is produced [71].

Also, *B. cinerea* invasion releases proteases in the berry, yielding an array of proteins, especially haze-active and proline-rich proteins [76,77]. The altered grape proteins affect wine properties such as gushing and foaming in sparkling wine [78]. It produces gluconic, glucuronic and galacturonic acids through the degradation of pectin compounds of the grape cell wall, which are considered *B. cinerea* indicators [73,76]. Moreover, enzymes that catalyze the oxidation of phenolic compounds are generated, mainly polyphenol oxidase including tyrosinase and laccase. Tyrosinase originates from grape berries, and laccase from *B. cinerea*. Tyrosinase and laccase hydroxylate and oxidize polyphenols to form brown pigments causing alteration of final wine color and flavor [79,80]. The laccase oxidizes a broad spectrum of polyphenols in must and wine: gallic, caffeic and ferulic acids or resveratrol [81].

Resveratrol has been reported to have antioxidant, anticancer, cardioprotective, and neuroprotective effects on human health [82,83]. Of interest, some resveratrol derivatives in botrytized must and wine are at higher levels than resveratrol following glycosylation, methoxylation or oxidative oligomerization reactions induced by *B. cinerea* secretome [84]. The resveratrol derivatives of piceid, pterostilbene and viniferins are the products of glycosylation, methoxylation and oxidative oligomerization, respectively, and have been detected in noble wine [85]. In addition, noble rot induces biosynthesis and the formation of lignin, stilbene and anthocyanins, which leads to the accumulation of polyphenols in botrytized wine. Thus, the formation of noble rot stimulates pathways leading to the accumulation of functional polyphenols, otherwise inactive in normal grape berries.

Moreover, the interaction of yeast fermentation with the noble rot results in a unique and complex profile of sweet botrytized wine, including specialty wine brands of *Tokaji* (in Hungary), *Sauternes* (in France) and *Trockenbeerenauslesen* (in Germany and Austria) [86,87].

6. Wine functional components and health benefits

Several studies have focused on the health benefit of wine than just an alcoholic beverage. If the functional components are released during maceration and/ or enhanced by wine microbiota during winemaking, their intake following moderate consumption of wine has a significant benefit on human health. Accordingly, studies have suggested that moderate red wine consumption reduces incidences of cardiovascular diseases and type 2 diabetes in comparison with other alcoholic beverages [88,89]. Wine contains an array of phenolic compounds that are antioxidants, which have shown a variety of health benefits. Nevertheless, wine has probiotic potential as contributed by a pool of microbial consortia during winemaking. Additionally, several health benefits may arise from other bioactive metabolites in the wine matrix (Fig. 1).

6.1 Wine polyphenols

Polyphenols in the grapes are mainly synthesized in the berry skin tissues and seeds. They are classified as flavonoids and non-flavonoids. The flavonoids include flavonols (kaempferol, quercetin, isorhamnetin and myricetin), the flavanols (catechin, epicatechin and proanthocyanidins), anthocyanins, dihydroflavonols and proanthocyanins [90]. Non-flavonoids are hydroxybenzoic acid, hydroxycinnamic acids (*p*-coumaric acids, caffeic acid and caftaric acid) and stilbenoids (resveratrol) [91]. Polyphenols are extracted into the wine during the maceration stage and winemaking process. However, their final concentration in wine depends on the grape type and contact of the must and solid part of the grape berries. During winemaking, factors such as microbes, physical and chemical properties of must have been demonstrated to modify the structure and concentration of polyphenols in wine. Moreover, fermentation processing has been reported to facilitate the release and enhance the accessibility of polyphenols from plant-based matrices as well as converting polyphenols into unique functional metabolites [92-94]. The improved and changed profile of phenolic compounds is mainly due to the release of bound phenolics as a consequence of degraded cell wall structure by microbial enzymes produced during fermentation as detailed in previous sections.

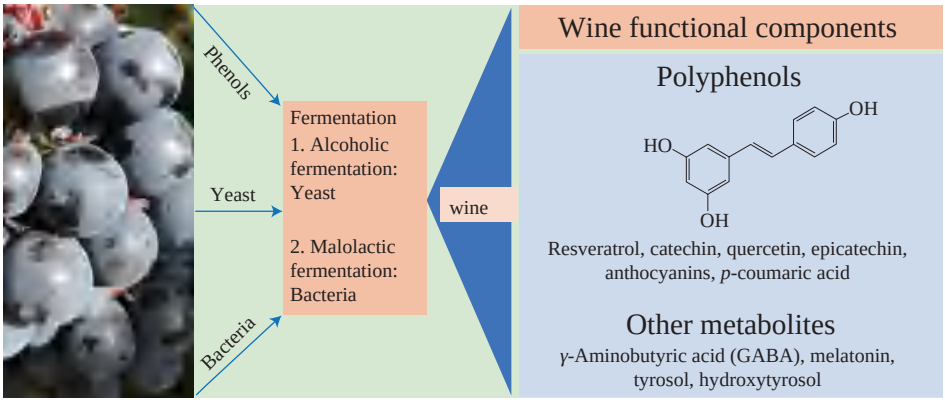

Fig. 1 Schematic illustration of alcoholic and malolactic fermentation of grapes for enhancing wine functional components.

Polyphenols play both direct and indirect impacts on wine quality. They contribute to the characteristics color and aroma of wine, act as natural wine preservatives and determine wine's functional properties as shown by various studies (Table 2). Resveratrol is considered to be part of the grape berry's defense mechanism, since it displays antimicrobial activities. Some of the reported resveratrol health benefits to human include anticancer and antidiabetic activity, reduction of insulin resistance and prevention of osteoporosis, neurodegenerative disorders, arteriosclerosis and heart diseases [95-97]. The polyphenol's antioxidant properties protect cell constituents from oxidative damage and thus limit the risks of developing neurodegenerative disorders such as ischemia, Parkinson's and Alzheimer's diseases. The anthocyanins offer protection against tumor development, cancer, cardiovascular diseases and metabolic syndrome [98]. The study by Damianaki et al. [99] revealed that red wine polyphenols in terms of resveratrol, catechin and epicatechin in the range of picomolar or nanomolar concentration displayed resistance and antiproliferative effect on breast cancer cell growth. For instance, several studies have reported resveratrol in a concentration range from 153 ng/mL to 2 616 ng/mL in wine [100,101]. Moreover, wine polyphenols provide neuroprotective function and protect the brain cells through scavenging intracellular reactive oxygen species (ROS) and inhibition of low-density lipoprotein (LDL) oxidation [102,103]. For instance, compounds with antioxidant properties were revealed to have therapeutic effects against melanoma cell lines *in vitro* [104].

Ferulic and *p*-coumaric acids can be metabolized by yeasts and LAB contributing to wine color and volatile phenols [105,106]. On the other hand, most of the non-*Saccharomyces* yeasts have a hydroxycinnamate decarboxylate activity that forms vinylphenolic pyranoanthocyanins, the stable pigment from hydroxycinnamic acids, which protects the wine from oxidation [107]. Phenolics are responsible not only for wine color, flavor and astringency, but also for certain functional properties such as induction of enzyme expression in most of the LAB [105]. For instance, malolactic fermentation by *O. oeni*, is activated by catechin or quercetin and inhibited by high levels of *p*-coumaric acid. Additionally, *O. oeni* glycosidases hydrolyze anthocyanins to various polyphenols, which enhances wine color and aroma [68,108]. To reveal the functional benefit of wine, the analysis of urine and fecal metabolome of a person who drank red wine revealed that wine polyphenols provide prebiotics function to gut microbiota [109,110]. Also, previous research works have associated increased diversity of intestinal microbiota with wine polyphenols following moderate consumption of wine [13]. Thus, wine polyphenols can modulate the gut microbiome to produce specific functional metabolites that benefit human health. It has been estimated that, 5%–10% of ingested polyphenols are absorbed in the small intestine and the remaining 90%–95% reach the colon and are subjected to hydrolysis and degradation by the colon microbiota into a diverse range of bioactive phenolic metabolites, phenolic acid and lactones, which are further reabsorbed [102,103]. They are absorbed through the gut barriers and extensively metabolized in different tissues of the small intestine, colon and liver. Indeed, the alteration of wine polyphenols into metabolites and other derivatives constitutes a true bioactive.

6.2 Wine prebiotics potential and other metabolites

The functional properties of wine are not only attributed to polyphenols, but also the prebiotic potential and other microbiota

Table 2
Wine functional components and their corresponding health benefits.

Wine functional components	Health benefits	References
Polyphenols	· Possess antioxidant, anti-thrombotic and anti-inflammatory activities and therefore decrease risks of heart attack, hypertension and certain types of cancer. · Increase activities of detoxifying and antioxidant enzymes. · Protect cognitive function and may reduce neurological disorders such as dementia and Alzheimer's diseases. · Regulate lipid metabolism and associated with increased levels of high-density lipoprotein and delays or inhibits atherosclerosis. · Have a prebiotic function and promotes the proliferation of intestinal microbiota. · Have antimicrobial activities in the gastrointestinal tract and respiratory system. · Inhibitory effect on α-amylases and α-glucosidases preventing hyperglycemia and type 2 diabetes.	[110-114]
Other components		
Melatonin	· Provides antioxidant and anti-inflammatory effects, a potent radical scavenging compound and regulates the antioxidant enzymes. · Has neuroprotective effects and reduces oxidative injury in the central nervous system. · Is effective in the control of hypertension and metabolic syndrome. · Controls sleep and circadian rhythms.	[115-117]
γ-Aminobutyric acid (GABA)	· Provides inhibitory role in neurotransmission in the central nervous system and protects neurodegenerative diseases: dementia, seizures, Alzheimer's and Parkinson's diseases. · Plays a role in reducing physical fatigue, sleeplessness and depression. · Improves mental focus and task solving ability. · Regulates blood pressure of hypertensive individuals by producing a hypotensive effect. · Improves immune function. · Inhibits or delays metastasis of various cancer cells of breast, colon and liver cancer.	[118,119]
Hydroxytyrosol	· Provides antioxidant and anti-inflammatory effects. · Prevents and reduces lipid peroxidation. · Has a neuroprotective effect and attenuates diverse neurodegenerative disorders: dementia, Alzheimer's and Parkinson's diseases. · Promotes cardiovascular health benefits · May prevent metabolic syndrome as well as cancers and type 2 diabetes.	[116,120,121]

metabolites. Wine microbiota's ability to synthesize and generate metabolites such as GABA and folate (vitamin B_9) gives wine anti-aging, anti-inflammatory and anti-cancer properties [122,123]. Evidently, GABA and a range of amino acids had been detected in wine from different region [124,125]. For instance, GABA in the range of 1.46–444 and 1.33–61.44 mg/L in white and red wine, respectively has been revealed [126]. Also, the study which, employed *O. oeni* and *Lactobacillus plantarum* (currently *Lactiplantibacillus plantarum*) to perform malolactic fermentation reported increased GABA concentration in the wine after malolactic fermentation [127]. Noteworthy, delaying nerve cells senescence, repairing skin, lowering blood pressure, regulating cardiac arrhythmia and treating mental illnesses are the reported physiological function of GABA in human health.

Moreover, wine *Lactobacillus* spp., *O. oeni*, *Pediococcus acidilactici* and *Pediococcus parvulus* were reported to produce exopolysaccharides, which gives the wine a prebiotics function [128-130]. Although, grapes variety influences the quantity, composition and structure of wine oligosaccharides, microorganisms play a role in their final fractions as was previously revealed in Cabernet Sauvignon, Syrah and Monastrell wines [131]. Also, *O. oeni* may produce melatonin, a neurohormone in the regulation of circadian rhythms and a strong antioxidant [132]. Similarly, *S. cerevisiae* strains and non-*Saccharomyces* including *M. pulcherrima* and *T. delbrueckii* were reported to synthesize melatonin in wine [133]. Evidently, melatonin has been reported in wine up to a concentration of 423.01 ng/mL [134,135]. Moreover, a significant increase in gut microbiota as well as controlled blood pressure and cholesterol were reported following consumption of red wine or fermented food rich in dietary phenolic compounds [92,136]. In comparison with other fermented food, Li et al. [92] revealed that polyphenol extract from pickled radish modulated gut microbiota composition and significantly reduce serum lipid levels in animal experiment. In an intervention study, Zorraquín-Peña et al. [137] revealed that moderate wine consumption increased fecal phenolics and short-chain fatty acids, and provided a prebiotic function to the intestinal microbiota. Also, supported by the cohort study that involved female individuals in the United Kingdom, which came up with the conclusion that red wine consumption was associated with increased diversity of gut microbiota [138]. Therefore, moderate consumption of wine can inhibit non-beneficial bacteria from the human microbiota pool and stimulate the proliferation of the beneficial ones.

7. The concept of light to moderate wine consumption and a standard drink

Consuming wine to have significant health benefit might involve a sufficient amount hence a standard drink is advised to minimize the effect of alcohol on human health. A standard drink is an amount of alcohol an average adult can metabolize in one hour, since the rate differs per individual's weight, height, age, sex, degree of adiposity as well as race [139,140]. In the United Kingdom and Iceland, a standard drink is defined as an alcoholic beverage containing 8 g or 10 mL of pure alcohol; France, Australia, the Netherlands and Spain consider a standard drink as 10 g or 12.5 mL of pure alcohol, while the United State and Korea consider 14 g or 17.5 mL of pure alcohol as a standard drink [140-142]. Generally, these amounts can be translated into 125 mL of table wine of 12% ethanol. However, moderate wine consumption may vary from country to country because of typical serving sizes. For instance, the American Dietary Guidelines Advisory Committee considers a moderate alcohol intake by an adult of legal drinking age as a daily amount consumed $\leq$ 10 g of ethanol ($\leq$ 1 drink) for women and $\leq$ 20 g of ethanol ($\leq$ 2 drinks) for men [140]. Of the various drinking patterns, daily low to moderate dose alcohol intake, particularly red wine before or during the evening meal, is associated with a significant reduction in adverse cardiovascular outcomes [141,143]. In addition to a standard drink, it is recommended to drink no more than two standard drinks per day and no more than five days per week [144].

8. Wine and food safety

Wine may contain contaminants, including pesticides and chemical preservatives such as sulfites, biogenic amines allergens, as well as possible carcinogens such as mycotoxins (ochratoxin A) and ethyl carbamate [145]. Residues of pesticides, sulfite, mycotoxins and heavy metals have been detected even in the strict winery environment. However, in terms of pathogens, wine is considered a low-risk food due to its high polyphenol content, low pH, acidic and alcoholic environment, which synergistically prevent the growth and proliferation of foodborne pathogens.

Second to cereals, wine is the major source of ochratoxin A, which is produced by *Aspergillus* and *Penicillium* on the grapes [146]. Ochratoxin A, a mycotoxin linked to chronic nephropathy has been reported in wines from different regions [147,148]. On the other hand, pesticide residues were reported in the wine produced in different regions, although at values below the maximum residue levels (MRLs) [149,150].

For improving wine safety, biocontrol of diseases in the vineyard can be achieved by the use of antagonistic yeast and bacteria, to eliminate pesticides or limit their use to the minimum. Also, the application of wine intrinsic factors such as yeast, bacteria, bacteriocins and polyphenols to control wine spoilage microorganisms can eliminate or reduce the application of sulfur dioxide (SO_2), which is intolerable to some individuals and produce adverse health reactions [151]. Although, the use of SO_2 is not limited to their antimicrobial potential, but also for binding different compounds and providing antioxidative impact.

Biogenic amines in wine are formed from precursor amino acids, mainly via microbial decarboxylation, transamination and/ or degradation of certain precursor amino acids during different stages of winemaking [145,152]. Histamine, tyramine, phenylethylamine, putrescine and cadaverine are the frequent biogenic amines in wine. Their presence in wine plays a vital role because high amounts of them can lead to health problems in human including headache, impaired breathing, hypertension or hypotension, blushing, itching,

vomiting and skin irritation, in addition to spoilage of wine [153]. The biogenic amines in wine can be controlled by eliminating spoilage bacteria, reducing the precursor amino acids (histidine, tyrosine, lysine, phenylalanine and tryptophan) and selecting yeast and bacteria that produce low amounts of the amines during alcoholic and malolactic fermentation [154]. Moreover, the use of microbes with the ability to utilize or degrade biogenic amines was previously discussed.

Therefore, wine as food needs public attention on food safety and traceability. Traceability ensures safe food supplies and connects producers and consumers on the information of product, process, input, measurement, pests and disease. It can be achieved through bar codes, alphanumerical codes and radio frequency identification such that consumers can easily trace the origin and overall process of wine and verify the authenticity and genuineness of a particular wine [155].

9. Conclusion

Wine microbes play an important role in the oenological research and industries to innovate and produce wine with enhanced functional components. The emergence of low-alcohol wine in the market and wines with healthy antioxidants from polyphenols have attracted customer's attention. Besides polyphenols, wine microbiota metabolites may benefit human health. The autochthonous wine *Saccharomyces*, non-*Saccharomyces* yeasts, bacteria and fungi have not only improved the wine functional properties through increased antioxidants, polyphenols and prebiotics function to gut microbiota, but also, contributes to wine color stabilization, control of spoilage microorganisms and alcohol reduction. In that regard, wine provides a variety of functional metabolites, which synergistically impact human health. Therefore, this review unlocks opportunities to understand better the applications of wine microbiota and their metabolites to increase the sensible functional characteristics other than just an alcoholic beverage. Bringing all together, wine like other food should be consumed in an amount beneficial to human health.

Conflict of interest

The authors declare that they have no conflicts of interest.

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