Yeasts on Fermentation Quality and Human Health-Promoting Compounds

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Non-*Saccharomyces* are important during wine fermentation once they influence wine composition. In the early stages of wine fermentation, and with indigenous or commercial Saccharomyces cerevisiae strains, non-*Saccharomyces* can transform grape-must sugars into ethanol, CO_2, and other important secondary metabolites. A better understanding of yeast biochemistry will allow the selection of yeast strains that have defined specific influences on fermentation efficiency, wine quality, and the production of human health-promoting compounds. Yeast metabolism produces compounds derived from tryptophan, melatonin, and serotonin found in fermented beverages, such as wine and beer. Melatonin is a neurohormone secreted from the pineal gland and has a wide-ranging regulatory and neuroprotective role, while serotonin, as well as being a precursor of melatonin synthesis, is also a neurotransmitter.

Keywords: Yeasts ; resveratrol ; glutathione ; trehalose ; tryptophan ; melatonin ; serotonin ; tyrosol ; tryptophol ; hydroxytyrosol

1. Introduction

The term “fermentation” comes from the Latin word “*fermentum*” (meaning to ferment). The science of fermentation is called “zymology” and the first zymologist was Louis Pasteur, who could identify and apply yeast in fermentation [1]. Food fermentations date back at least 6000 years. In the 16th century, the beginning of industrialization initiated technological interventions in food and beverage production [2]. However, it was in the last two centuries that significant changes in the world’s food system have occurred. In the olden days, the fermentation of food was meant for food preservation and flavor improvement [3]; nowadays, in food and beverage fermentation, various technologies and operations are used to convert fairly perishable and indigestible raw materials into pleasant foods and drinkable beverages with added value and high stability [4]. The assurance of the quality and safety of the final product is the primary goal of the technologies applied [5].

Biotechnology plays a radical role in food production, conservation, nutritional enrichment, and value addition. Understanding the science of microbiology in food and beverage applications with the identification of new-fermenting species is an advantage to enhance the quality of our food products.

Food and beverage processing using microorganisms is the most suitable technology for developing innovative fermented food products. Solid-state fermentation is used for the processing of vinegar, soy sauce, tea, and cheese [6]. Wine, beer, distilled beverages, and yogurt are developed by submerged fermentation.

2. Alcoholic Beverages Consumption and Health-Promoting Compounds

Preventing diseases by altering lifestyle and dietary conduct may present more benefits than medical care. Up till now, adjusting individual nutritional habits has been a challenge. Consumers must often choose between nutrition, taste, price, convenience, and cost [7]. Nowadays, the nutritional value appears to be the health benefit that most impacts a consumer’s purchase [8].

Oxidative stress and antioxidant deficiency have been implicated in the pathogenesis of many diseases and conditions, including atherosclerosis, cancer, aging, and respiratory disease. Glutathione (L-g-glutamyl-L-cysteinyl-glycine, GSH) (**Figure 1**) is a significant antioxidant acting as a free radical scavenger that protects the cell from ROS (reactive oxygen species). In addition, GSH is involved in nutrient metabolism and regulation of cellular metabolic functions ranging from DNA and protein synthesis to signal transduction, cell proliferation, and apoptosis [9][10][11].

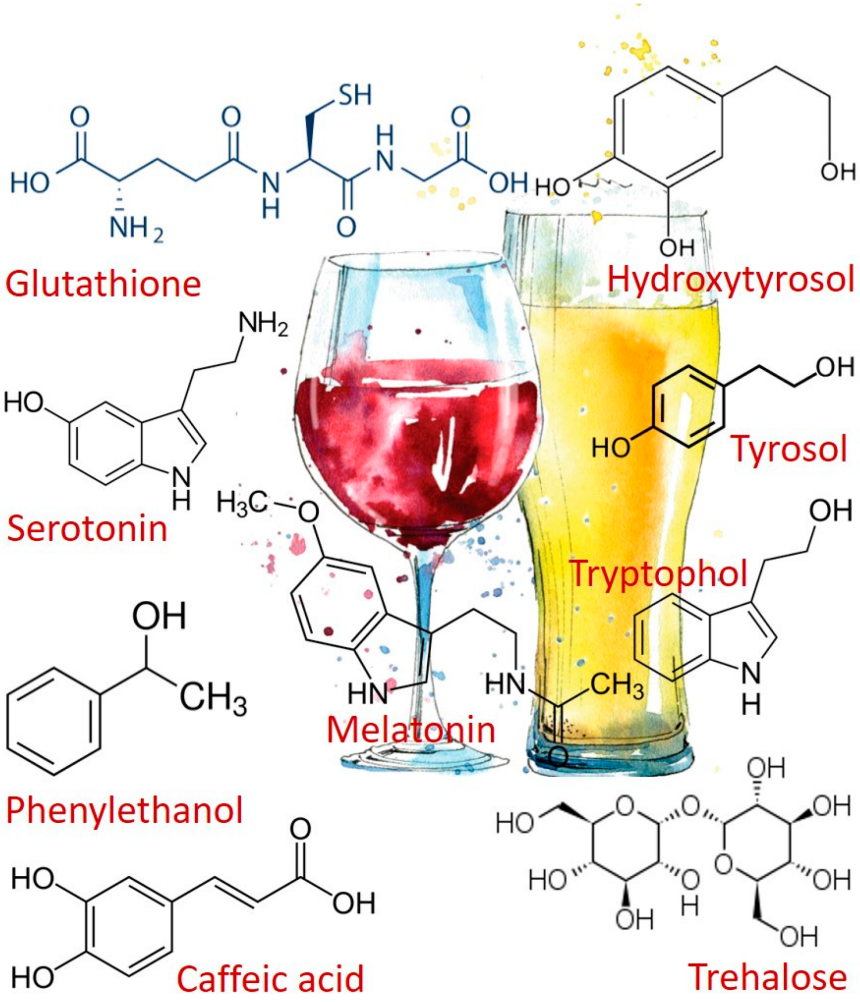

Figure 1. Chemical Structures of the health-promoting compounds mentioned.

Another vital molecule is trehalose (**Figure 1**). This sugar also possesses inflammatory properties [12], presenting the ability to protect cellular membranes and labile proteins against denaturation due to desiccation and oxidative stress [13].

Yeast metabolism produces compounds derived from tryptophan in fermented beverages, such as wine and beer. In particular, melatonin and serotonin (**Figure 1**). Serotonin is a neurohormone that regulates circadian rhythms and also has an alleged protective effect against neurodegenerative and degenerative diseases (Alzheimer's, Parkinson's, and Angiogenesis) [14]. Moreover, serotonin is a neurotransmitter itself and a precursor of melatonin synthesis.

In humans, melatonin (N-acetyl-5-methoxytryptamine) is a hormone that modulates several physiological processes. This molecule is an indole amine found in many living organisms like plants, microorganisms, and humans. Melatonin modulates many human physiological processes, including the sleep/wake cycle and the reproductive physiology via a receptor-mediated mechanism [15][16], acting as an antioxidant via nonreceptor methods [17]. It is well known that the intake of foods containing melatonin increases its level in plasma and the number of melatonin-derived metabolites [18]. Studies have identified melatonin in grapes [19] and beverages such as beer and wine [20][21]. Interesting is the reported concentrations of melatonin in grapes (*Vitis vinifera* L.) and wines: 150 µg/g in Merlot grapes [22]; and 130 ng/mL in Tempranillo wine [23].

Tyrosol and tryptophol (**Figure 1**) are produced by yeasts during alcoholic fermentation from the catabolism of the amino acids tyrosine and tryptophan, respectively. In contrast, hydroxytyrosol is produced by the hydroxylation of its precursor, tyrosol. Tyrosol, hydroxytyrosol, and tryptophol are reported to possess several health-enhancing activities, deriving from their free radical scavenging, anticarcinogenic, cardioprotective (induces myocardial protection against ischemia-related stress [24]), and antimicrobial properties [25].

Due to the presence of tyrosol and caffeic acids (**Figure 1**), white wine has been reported as having cardioprotective benefits. Tyrosol and caffeic acids can activate the cell survival signaling pathway and the *FOXO3a* longevity-associated gene [26][27]. Moreover, tyrosol has been shown to have an essential role in the taste of some alcoholic beverages, such as sake [28] and wine [29], exhibiting a bitter taste above the sensory threshold but below the recognition threshold.

Tryptophol is also a precursor in synthesizing Indoramin, an α-adrenoreceptor blocking drug used to treat hypertension [33] and benign prostatic hyperplasia [30].

Phenylethanol (**Figure 1**), also produced by *Candida albicans* as an auto-antibiotic [31] is an aromatic compound commonly found in plants, such as roses, possessing a pleasant floral rose-like odor. Due to its preservative properties, phenylethanol is often used in soap-based detergents because of its stability in primary conditions. Phenylethanol can also be a natural preservative in wine and beer to prevent spoilage [31].

3. Mechanisms of Microbial Resistance to Environment Changes that Produce Health-Promoting Compounds

Conservation and commercialization of yeast cultures in fresh liquid or pressed forms are not economically advantageous. Thus, dehydrated yeasts present numerous advantages, such as lower cost, convenience for transport and storage, and ease of handling [32]. However, drying the yeasts signifies susceptible transformation processes for microorganisms which can lead to cell death or a significant decrease in cell activity potential [33]. The final water volume of the cells, induced by dehydration-rehydration cycles, influences the cell's survival [34], and the modification of plasma membrane fluidity during the dehydration-rehydration cycles affect the plasma membrane structure and may induce cell mortality [35].

An increase of contact surface of the cells with air during dehydration also induces accumulation of ROS (reactive oxygen species)—[$O_2^{\bullet-}$ (superoxide anion), $^{\bullet}OH$ (hydroxyl radical), H_2O_2 (hydrogen peroxide) and ReOOH (hydroperoxides)]—and may contribute to inactivation of several enzymes, leading, also, to cell death [36]. In these stress conditions, yeasts can synthesize compounds such as glutathione and trehalose [37].

Glutathione (GSH) is a ubiquitous low molecular weight thiol tripeptide containing glutamate, cysteine, and glycine (Glu-Cys-Gly). It is present in large amounts in yeasts and it can be found in the reduced or oxidized forms (GSH and GSSG, respectively). Glutathione plays a crucial role in redox equilibrium reactions, protecting the cell from oxidative stress by allowing the formation of native disulfide bonds and by scavenging free radicals present in the cytosol; responses mediated via glutathione reductase and glutathione peroxidase [9][38].

Hgt1p in yeast *S. cerevisiae* was the first identified high-specificity and high-affinity glutathione transporter (Km 54 mM) [39]. Hgt1p belongs to the oligopeptide transporter family, also found in fungi, plants, and prokaryotes. Genetic and physiological investigations revealed that gene *HGT1* (open reading frame *YJL212c*) encodes a high-affinity glutathione transporter. Yeast strains deleted in the *HGT1* gene showed no detectable plasma membrane glutathione transport. This transporter is required to uptake glutathione from the extracellular medium [39]. Moreover, mitochondria are a primary source of ROS in cells, and mitochondrial thiols are, therefore, primary ROS targets. The relatively alkaline pH of mitochondria exacerbates this phenomenon. Therefore, redox regulation is critical for numerous mitochondrial functions, and yeast strains lacking GSH are unable to grow by respiration due to an accumulation of oxidative damage to mitochondrial DNA. The transport of H_2O_2 across yeast cell membranes can be facilitated by transporters such as aquaporins. Hydrogen peroxide causes oxidative stress but also plays an important role as a signaling molecule in regulating many biological processes [40].

Thiol redox regulation plays a role in the response of cells to oxidative stress conditions. Gostimskaya and Grant [41] emphasize the importance of compartmentalized redox regulation when cells are subjected to oxidative stress conditions. At the same time as cytosolic glutathione represents the first significant pool of thiols, which would be a target of oxidation in response to exposure to an exogenous oxidant, the mitochondrial glutathione pool is crucial for oxidant tolerance.

4. Melatonin and Other Tryptophan Metabolites

In the scientific world, the theme of “wine and health” topics has been focused mainly on polyphenols once these bioactive compounds are present in plants and are released into fermented products. However, yeast also transforms other molecules into biologically active compounds [16]. Since the pioneering work of Sprenger and co-workers [42], the melatonin molecule has been reported as being present in wine, and its presence has been related to the activity of the yeast involved in the fermentation process. Initially seen as a unique product of the pineal gland of vertebrates called a neurohormone, it is currently considered a ubiquitous molecule in most living organisms [43].

Rodriguez-Naranjo and co-workers [23] studied the capacity of different yeasts to produce melatonin during alcoholic fermentation. Different *Saccharomyces* yeast strains, used for industrial fermentation of beer or as nutritional complements and non-*Saccharomyces* yeast strains (*Metschnikowia pulcherrima* and *Starmerella bacillaris*) were tested

by the referred authors to analyze intracellular and extracellular melatonin production in synthetic grape must. Interestingly, melatonin was detected in the intracellular compartment at the beginning of fermentation, either in *Saccharomyces* or in non-*Saccharomyces* strains. Production levels differed among strains; *Starmerella bacillaris* the non-*Saccharomyces* yeast, presented the highest concentration. Nevertheless, depending on the yeast strain, extracellular melatonin was detected at different time points over the fermentation process. However, the same authors [23] also reported that tryptophan is essential for melatonin production since it is its principal precursor; it increases final melatonin content and accelerates its formation. Moreover, the synthesis of melatonin largely depends on the growth phase of the yeast and the concentration of the reducing sugars.

The metabolic pathway for melatonin production in yeast is not entirely clarified; nevertheless, the formation of serotonin might be an intermediate metabolite in the pathway [16].

5. Fusel Alcohols Formed Via the Ehrlich Pathway

The synthesis of tryptophol by yeast was first described by Felix Ehrlich in 1912 [44][45] as the metabolic conversion of amino acids via the successive steps of transamination, decarboxylation, and reduction [46].

Similarly, tryptophol, phenylethanol, and tyrosol are phenolic compounds or fusel alcohols formed via the Ehrlich pathway by yeast metabolism. These compounds can yield health benefits and contribute to the flavors and aromas of fermented food and beverages [45][47].

6. Fermented Beverages Containing Probiotics

It is common knowledge that most fermented milk contains probiotic microorganisms (live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host). Yogurt, the most common product of milk lactose fermentation, has several lactic acid bacteria in its constitution. So, the domination of milk-based beverages fermented by LAB, mainly *Leuconostoc*, *lactobacilli*, and *lactococci*, is apparent. Milk fermentation in colder climates promotes the growth of mesophilic bacteria such as *Lactococcus* and *Leuconostoc*. In contrast, beverages produced at higher temperatures usually have more significant counts of thermophilic bacteria such as *Lactobacillus* and *Streptococcus* [48][49]. Most probiotic bacteria often come from *Lactobacillus, Bifidobacterium,* or a cocktail of both [50].

Another class of fermented beverages is those made from cereals (maize, millet, barley, oats, rye, wheat, rice, and sorghum), where the natural microbial component is used to ferment grains. The microbial populations responsible for the fermentation of these beverages are not, yet, well characterized. Of several blends, it has been suggested that fermentation by *S. cerevisiae*, *Leuconostoc mesenteroides*, and *Lactobacillus confusus* produce the most palatable beverages [48].

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