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PROMISING BIOANALYTICAL APPROACHES TO WINE ANALYSIS

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12.1 Introduction

Grape and rice wines, which are the oldest beverages in the world, as well as nongrape fruit wines, are the sources of nutrients and good mood (Danner et al., 2017; Drori et al., 2017; Dias et al., 2017). Wine growing began in Western and Central Asia, Egypt, the Mediterranean, ancient Greece, Rome, and Israel, and from there it spread to Europe.

The quality of the wine determines its sensory properties, transparency, stability, and safety. The main sensory properties of alcoholic beverages are aroma, taste, texture, color, and viscosity (Jackson, 2014; Niimi et al., 2017). Natural wines are a good dietary source of minerals, such as potassium, calcium, and phosphorus; antioxidants, phenolic compounds, and phytonutrients (Villaco et al., 2006; Arcari et al., 2013; Lu et al., 2015). The basic components of wine that determine its quality are glucose, ethanol, glycerol, volatile compounds, vitamins, and proteins (Waterhouse et al., 2016; Jackson, 2014). It has been proven that the level and ratio of the basic components in the wine depend on the type of raw material (grape or rice variety, degree of its maturity and geographical region of its cultivation), the processing method, the beverage production, the conditions of maturation (holding), and the storage of the wine (Garde-Cerd and Ancin-Azpilicueta, 2006; Jones et al., 2008; Villamor et al., 2013; Jackson, 2014; Lu et al., 2015; Uríčková and Sádecká, 2015). The positive effect of natural wines on human organism was investigated for many centuries. The latest scientific experiments have demonstrated the beneficial health effects of moderate wine consumption (Lu et al., 2015; Danner et al., 2017;

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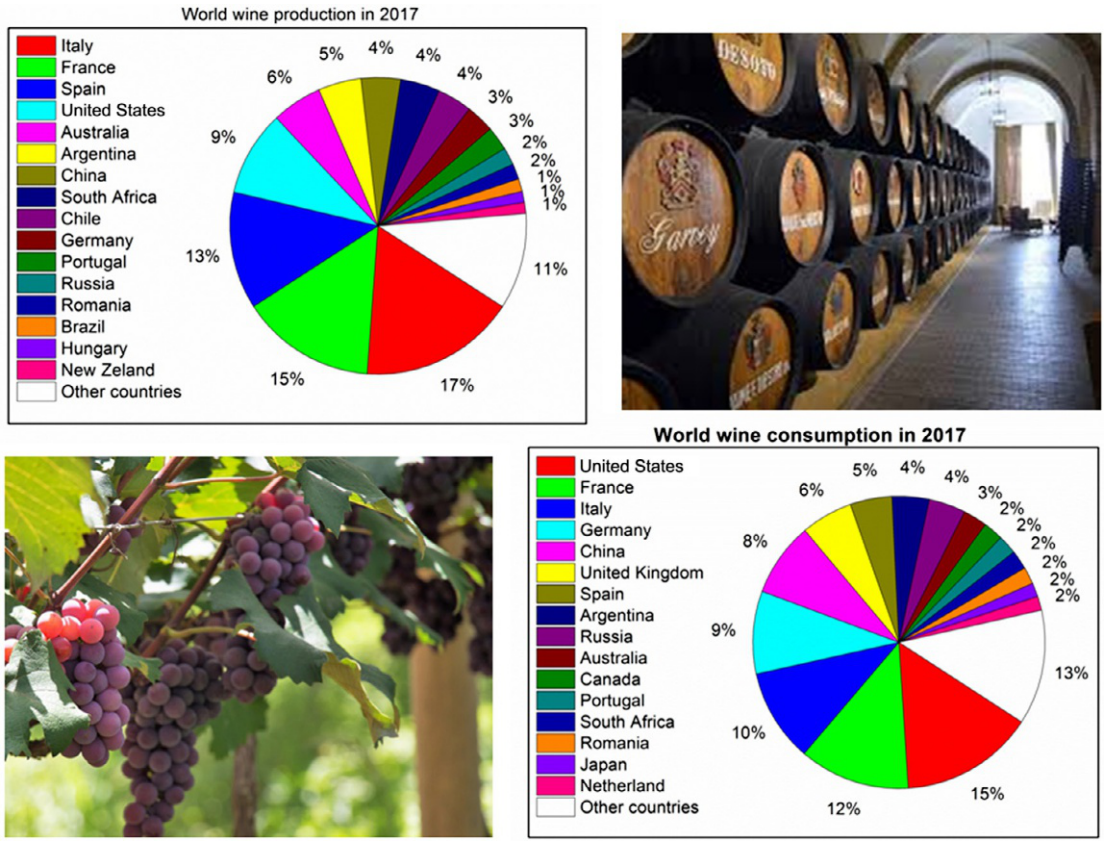

Fig. 12.1 Global wine production and consumption by country.

Lezaeta et al., 2017; Jackson, 2014; Rosenzweig et al., 2017; Martin et al., 2017). Fig. 12.1 illustrates the modern tendency of worldwide wine production and consumption.

Wine is a biological fluid and an inexhaustible subject of research. The outstanding chemist D. Mendeleyev stated, at the end of the 19th century, that: "All kinds of wine contains 95%–99% of water and alcohol, but in the remaining 5% chemistry has been found in such a variety of substances and in such small homeopathic doses that their effects on the body are far from being investigated; the difficulty of their study depends in part on the smallness of their content in wine. A 'bunch of wine' is still little known due to the great difficulties of its study and the great costs for this."

Different branches of natural science (traditional and modern) serve to winemaking with the aim to satisfy the high quality and safety of the final product. Agricultural sciences, microbiology, genetics, biotechnology, nanotechnology, biochemistry, analytical chemistry, analytical biotechnology, enology, physical chemistry, instrumentation—this list

is not final yet. Many scientific institutions and agro-industry associations are currently working on winemaking, which is a highly profitable food industry, aiming to ensure proper quality and safety of the products (or their improvement) and to expand the range.

Food safety in recent years is of a great concern and a priority area of attention for many countries (Lawley et al., 2008). European Commissioner (EC) for Health and Food safety in message for World Heart Day in 2017 has reported about the decision of EC concerning the mandatory labeling of the list of ingredients and the nutritional declaration for alcoholic beverages, which concludes that "EU citizens have the right to be fully informed about what they drink" (Andriukaitis, 2017). To ensure food safety and agricultural commodity trade, China has developed a regulatory system for the risk assessment and management of genetically modified products (Gao et al., 2018).

Wine is the final result of a long process of physical, chemical, and biological transformations. Every step of wine production is strongly affected on the quality and compositional features of the end product. Therefore, it is crucial for beverage industry to control the wine production chain—from the management of soil practices till the analysis of bottled wine (Waterhouse et al., 2016; dos Santos et al., 2017).

Winemaking therefore requires perfect analytical methods at every stage of the production process, and this is impossible without using the most modern and high-tech devices. The last methods require special skills, are time-consuming, expensive, and often also have low selectivity. Thus, further development of highly selective, sensitive, rapid, and reliable methods for identifying the key ingredients or metabolites which determine the quality of the product, as well as for monitoring wine contaminants to ensure the safety for human health, is an actual problem.

In this chapter, the main achievements in the elaboration of modern quantitative analytical methods for important components of wines are reviewed. The results of a series of the authors' investigations dealing with the development of novel highly selective enzymatic approaches, including biosensors, for determination of organic and inorganic analytes—mandatory components of wine, are summarized.

12.2 The Chemistry of Aroma and Taste

12.2.1 The Parameters Studied in Wine Science

The analytical parameters that are usually controlled in winemaking are physical (density, pH, density), microbiological (presence of desirable yeasts and bacteria, as well as contaminating microorganisms), sensory (product acceptance), and chemical. The list of chemical compounds, the objects of wine science, is the next: alcohol,

glycerol, fermentable sugar (glucose, fructose), total acid including organic acids (tartaric, malic, lactic, citric), volatile compounds (acids and esters), sugar-free extract, proteins (including enzymes), lipids, and inorganic compounds (Jackson, 2014; Waterhouse et al., 2016; Ruocco et al., 2017; Goold et al., 2017; McMahon et al., 2017; Dias et al., 2017; de Ovalle et al., 2018).

Wine is an extremely complex chemical composition, with >600 organic and inorganic components. From a macroscopic perspective, wine is a mildly acidic hydroethanolic solution: water and ethanol represent ~97% w/w of dry table wines. Ethanol is the major bioactive compound in wine and its presence renders wine and other alcoholic beverages inhospitable to microbial pathogens (Waterhouse et al., 2016). Alcohol is fundamental to the character of wine. An ideal wine is regarded to be well balanced if its alcoholic strength, acidity, sweetness, fruitiness, and tannin structure complement each other so that no single component dominates on the palate, but obtaining such perfect wine is a surprisingly difficult task (Goold et al., 2017).

Variations in the concentration of volatile compounds and ethanol impact the wine's aroma and taste, respectively. Fatty compounds, mainly ethyl esters of organic acids, appear as products of yeast metabolism during juice fermentation and create a "bunch of wine" (Waterhouse et al., 2016; Rangel and Tyth, 2000; Hu et al., 2018; Gammacurta et al., 2018). Global warming provokes a gap during grape ripening between phenolic maturity and sugar content. If grapes are harvested when the sugar content is appropriate but the phenolic maturity has not been reached, wines can show altered aroma, flavor, mouth feel, and astringency. On the contrary, if grapes are harvested when their phenolic maturity is the appropriate, their sugar contents are higher, giving rise to wines with increasing ethanol concentrations (Jones et al., 2008; Alonso-del-Real et al., 2017). This higher ethanol content is undesirable according to consumers' new demands, because affects flavor complexity sensing, and its excessive consumption is harmful for health and road safety (Goold et al., 2017; Alonso-del-Real et al., 2017).

The content of ethyl esters (isoamyl acetate, ethylhexanoate, ethyl octanoate, ethyldecanoate, etc.) in wine increases during the process of wine aging. It has been shown that certain concentrations of proteins, alcohol, and glycerol significantly affect several flavor notes (Waterhouse et al., 2016; Villamor et al., 2013; Jackson, 2014; Goold et al., 2017; de Ovalle et al., 2018). Polysaccharides somewhat weaken the intensity of the overall aroma, and glycerol contributes to the saturation of taste (Jones et al., 2008; Zhao et al., 2015).

Glycerol, as a major byproduct, serves critical roles in yeast osmoregulation and redox balancing, but also acts as the carbon competitor against ethanol in alcoholic fermentation. Therefore, increasing glycerol yield in wine benefits both the flavor intensity and

ethanol reduction. Both glycerol and polysaccharides affect the viscosity of the beverage (Zhao et al., 2015). Increased alcohol content enhances "unpleasant" textures of burning, tartness, and bitterness, while glycerol softens these effects (Goold et al., 2017).

Glucose is both a source of carbon for yeasts, which perform the fermentation, and a substrate limiting yeast growth. The amount of glucose fermented determines the ethanol content, and residual non-fermented glucose affects the sweetness of the wine. Monitoring levels of lactate, when producing high-quality beverages is obligatory since this parameter not only determines quality and flavor, but can also be used to control fermentation. Additionally, the stability of the wine during storage depends on lactate concentration (Jones et al., 2008; Jackson, 2014; Shkotova et al., 2016; Waterhouse et al., 2016).

12.2.2 Antioxidants

Evaluation of the antioxidant activity (AA) of components of the diet is important for establishing healthy consumption patterns (Villaco et al., 2006; Arcari et al., 2013; Lu et al., 2015). All wines contain antioxidants and phytonutrients such as carotenoids (carotene and lutein) and phenolic compounds (anthocyanins, flavonols, flavan-3-ols, proanthocyanidins, ellagitannins, and phenolic acids). It has been shown that red wines, in particular Cabernet varieties, have the highest AA, and that this activity increases with the increased duration of red wines' ripening during storage (Espinoza et al., 2009; Moreno-Montoro et al., 2015; Lu et al., 2015; González-Centeno et al., 2016).

Anthocyanins are the major natural flavonoid pigments in plant-derived food. These chemicals are thus the principal source for the red color in wine. Structurally, anthocyanins are glycosides and acylglycosides of anthocyanidins, the term for a simple flavonoid ring system. The common anthocyanidins found in grapes are cyanidin, delphinidin, peonidin, petunidin, and malvidin. The formation of polymeric anthocyanins with flavan-3-ols and proanthocyanidins and the development of pigmented tannins, such as pyranoanthocyanins and pinotins, increase as the wine ages, thus creating a stable pigment (Barnaba et al., 2017).

Metal ions greatly affect the properties of wines. Ions of transition metals, in particular copper and iron that were added to a wine sample in model experiments, reduce its antioxidant potential. The antioxidant potential is evaluated by electron spin resonance and spectrophotometric assay using the following free radicals: 2,2-diphenyl-1- picrylhydrazyl, galvinoxyl (2,6-di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadiene-1-ylidene)-*p*-tolyloxy), and hydroxyl. Wines' reducing ability for inactivating free radicals (namely, reducing the wine's antioxidant potential) is the result of an irreversible reaction of metal ions with polyphenols, with formation of inactive

complexes (Ragazzo-Sanchez et al., 2008; Elias and Waterhouse, 2010; Kontoudakis et al., 2017). In order to prevent loss of the healing properties of wine, it is important to know how to use it. In a model investigation, it was shown that the simultaneous presence of red wine and iron ions in the stomach leads to a decrease in the antioxidant potential of the wine's phenolic compounds due to their interaction, especially in the presence of meat proteins (Villaco et al., 2006).

12.2.3 Inorganic Compounds

Wines contain 1.5–3.5 g/L of different inorganic chemicals. Mineral compounds, in particular the cations K^+ (0.4–1.8 g/L), Ca^{2+}, Na^+, and Mg^{2+} (up to 0.2 g/L each), as well as sulfate anions (up to 1.0 g/L) and phosphate anions (up to 0.9 g/L), are found in wine as free ions or in complexes with organic components (Kontoudakis et al., 2017). Metals are present in foods (including drinks) either naturally or as a result of human activities such as agricultural practices, industrial emissions, car exhausts, or contamination during manufacture (Lawley et al., 2008). Yeasts need potassium ions, magnesium, manganese, iron, and phosphorus as cell growth factors. Iron and copper ions are also involved in oxidation-reduction reactions as catalysts. Depending on the type of wine, the total iron content is from 1.72 to 5.48 mg/L (Ajtony et al., 2008). An excess of metal compounds leads to undesirable changes in the fragrance and taste, which is why their content in wines is carefully controlled and limited: copper should not exceed 2.0 mg/L and iron should not exceed 10 mg/L. The concentrations of calcium, iron, chlorine, and sulfates in wines increase due to violations of the beverage production technology. Boron, iodine, rubidium, fluorine, manganese, and other substances are usually present in wines as trace elements and have, despite trace amounts, a significant physiological effect on the human body (Jones et al., 2008; Ajtony et al., 2008; Villamor et al., 2013; Arcari et al., 2013). Metallic ions in dependence of their contents affect greatly on the properties of wines. Ions of transition metals, in particular, copper and iron, being added to the sample of wine in model experiments, can reduce AA of wine. Copper was shown to affect accelerated rates of SO_2 consumption in the presence of iron and a polyphenol as well as metal haze formation as a result of reaction with tannin (Waterhouse et al., 2016).

Volatile sulfur compounds (VSCs) such as hydrogen sulfide (H_2S) have a significant influence on wine aroma as well as on post-bottling wine quality. H_2S is present in wine in both free and bound forms and the percentage of both forms are related to the trace metal content of the wine, especially of copper ions. VSCs contribute an undesirable impact when present at concentrations greater than its odor threshold

value of 1.1–1.6 μg/L, but in low concentrations H_2S can add complexity to wine aroma (Bekker et al., 2016).

12.2.4 Undesirable or Dangerous Impurities

One of the indicators of beverage quality is the absence of contaminants, which affect negatively to wine test, odor, or are dangerous for human organism.

The key chemicals responsible for olfactory defects in wine are volatile phenols, biogenic amines (BA), and sulfur compounds. Their appearance in wine is the result of poor control of raw material or nonstandard conditions of wine's fermentation and storage. Microbial contamination in all stages of winemaking is the most crucial reason of wine's degradation (Pena-Gallego et al., 2012; Kheir et al., 2013; Bekker et al., 2016; Ordóñez et al., 2017; Nalazek-Rudnicka and Wasik, 2017).

Monitoring of toxic and carcinogenic urethane or ethyl carbamate (EC) in fermented food products, especially in wines and other alcoholic beverages, is an important challenge for science and practical technology.

EC is a product of spontaneous reaction of urea with ethanol in the beverage under nonstandard technology conditions (Jiao et al., 2016; Zhao and Jiang, 2015; Luo et al., 2017). Current voluntary limit of EC in the United States was estimated as 15 μg/L, Canada and the Czech Republic have legalized this limit to 30 μg/L. France, Brazil, Germany, Switzerland, and China also control the EC level in some alcoholic drinks last years (Jiao et al., 2016; Gayda et al., 2015).

Two types of preventive methods for decreasing the EC levels in beverage food have been described: (1) adapted and optimized practices in all steps of the food (or beverage) production chain generally lead to low EC levels; and (2) the abatement of EC precursors can be achieved by adapted enzymatic, physicochemical, or chemical methods according to the nature of the raw materials and the conditions of their production processes. Thus, to ensure the high quality of food product and to avoid potential health hazard of EC, quantitative analyses of its precursor L-arginine (Arg) in fruit juices and wines is essential (Jiao et al., 2016; Zhao and Jiang, 2015; Luo et al., 2017).

12.3 The Analytical Methods Commonly Used in Winemaking

12.3.1 Traditional Methods

The traditional methods for analysis of the basic wine components which are described in the literature are chemical, physicochemical, and biochemical methods. These approaches are based on the use

of modern, in particular photometric and chromatographic, equipments. High-performance liquid chromatography (HPLC), molecular- sieve chromatography, gas-chromatography (GC), GC coupled with mass-spectrometry (GC-MS), affinity chromatography based on immobilized enzymes, atomic and molecular adsorption spectroscopy, electronic nose-like sensors—this is the list of methods that are commonly used in winemaking or are promising for this industry (Fernandes et al., 2004; García et al., 2006; Ajtony et al., 2008; Ragazzo-Sanchez et al., 2008; Jackson, 2014; Loutfi et al., 2015; Waterhouse et al., 2016). Unfortunately, the classical targeted measurement of compounds in wine using GC-MS is laborious and only a limited number of compounds can be quantified at any time (Schmidtke et al., 2013).

Enzymatic approaches, being rather simple and low-cost, can be promising for monitoring chemicals (enzymes substrates and their cofactors) in routine assay not only for the industrial giants, but also for small wineries (Rangel and Tyth, 2000; Mataix and de Castro, 2000; Segundo and Rangel, 2002; Ricci et al., 2007). Enzymatic bioanalysis plays a vital role throughout the whole of the winemaking process. Before the alcoholic fermentation, the nutritional status of the grape juice (yeast available nitrogen and the principle fermentable sugars) is determined. During the alcoholic fermentation, the levels of acetic acid (as the marker of infection by *Acetobacter* sp.), of urea (as the marker of forming the carcinogen EC), of acetaldehyde, ethanol, glycerol, succinic, L-malic acid, and L-lactic acids need to be controlled (Arvanitoyannis, 2010; Dias et al., 2017; Jackson, 2014; Waterhouse et al., 2016).

Biotechnological mega-companies, such as Megazyme, produce and supply an extensive and continually expanding portfolio of enzymes, mostly recombinant, for laboratories around the world. Megazyme is a global leader in the market of analytical enzymes and analytical kits for the determination of acetaldehyde, ethanol, glycerol, ethanol/glycerol ratio, monosaccharides, organic acids, and urea in winemaking. These kits are based on enzymatic-chemical methods with UV and fluorescence detection of the final product (https://secure.megazyme.com).

12.3.2 Biosensors

Biosensor is a hybrid device that contains two functional parts: a bioelement (biorecognition unit)—an immobilized biologically active material, and a physical transducer (signal converting unit). Numerous enzyme- and cell-based biosensors, being rapid and affordable instruments for ensuring the quality of products, have been described for the assay of various components during fermentation processes in winemaking and other biotechnological processes (Gonchar et al., 2017). Electrochemical biosensors, being simple, cost effective, highly sensitive, and selective may be a promising alternative to high-tech devices in wineries.

Enzyme biosensors are the most widely used devices, and some are produced commercially. The world biosensors market was estimated at approximately $11.39 billion in 2013, and is expected to reach $22.68 billion by 2020, with an annual growth of 10% from 2014 to 2020 (http://www.marketsandmarkets.com/PressReleases/biosensors.asp). Cell-based biosensors consist of a transducer in conjunction with immobilized viable or nonviable microbial cells, which are an economical substitute for enzymes (Gonchar et al., 2017). The target analyte is usually either a substrate or an inhibitor of cell metabolism. Cell biosensors have several considerable advantages compared to their enzyme analogues: availability of cells, low price, and simple procedure of cell isolation, possibility of using long metabolic chains, no need for purification of enzymes and coenzymes, advanced opportunity for genetic manipulations of metabolic pathways, and in some cases, higher stability of cell elements compared to enzymes (Gonchar et al., 2002, 2017).

Biosensors are based on the principles of biomolecular recognition, with spectrophotometric, chemiluminescence, fluorescence, amperometric, potentiometric, etc. modes of detection. Tissues, cells, organelles, biomolecules, and their complexes are used as biorecognition elements in biosensors. Different practically important analytes, including organic and inorganic compounds, toxins and microorganisms, may be tested by these highly selective devices (Nikolelis and Nikoleli, 2016; Gonchar et al., 2017). Different types of biosensors, promising for monitoring of the basic components of wines, namely, ethanol, glycerol, glucose, L-lactate (Gonchar et al., 2002, 2017; Smutok et al., 2011; Angeloni et al., 2015; Shkotova et al., 2016), as well as dangerous contaminants—L-arginine, as precursor of carcinogenic EC (Saiapina et al., 2012; Sheliakina et al., 2014; Gayda et al., 2015; Nikolelis and Nikoleli, 2016; Verma et al., 2017b; Dagar and Pundir, 2017; Soldatkin et al., 2017; An et al., 2017), other toxic chemicals, including pesticides, hormones, heavy and transitional metal, which penetrated in wine as a result of environmental (water, soil, air) pollution, were described recently in more detail (Gonchar et al., 2017; Gayda et al., 2017).

Biosensors provide many advantages in comparison to standard analytical detection methods such as minimal sample preparation and handling, faster time analysis, simpler steps of analysis, rapid detection of the analytes of concern, use of nonskilled personnel, and portability. In the last few years, nanotechnology approaches have been successfully used for the improvement of functional properties of enzyme- and cell-based sensors, namely, sensitivity, selectivity, and fastness of the analytical procedure (Han et al., 2015a,b; Xiang et al., 2015; Zeng et al., 2016; Morata et al., 2016; Lu et al., 2017; Dagar and Pundir, 2017; Mukherjee et al., 2017; Verma et al., 2017a). With the aim

to increase enzymes' local concentrations and to enhance the stability of biosensor, biocatalyts (cell or enzyme) were immobilized on the surfaces of nanoparticles (NPs) of noble metals (Stasyuk et al., 2014b, 2015, 2017a; Karkovska et al., 2015, 2017).

12.3.3 Modern Physicochemical Methods

In the last decades, new promising approaches for practical use of quantitative high-throughput methods are currently used, alongside traditional methods. Continuous improvements in technology, instrumentation, and chemometric methods indicated the possibility of replacing some of the current standard analysis methods, which can be time consuming, expensive, and labor-intensive, with automated vibrational techniques capable of in situ and real-time measurements, with a similar, or improved level of precision and accuracy (dos Santos et al., 2017; Pinzaru and Magdas, 2017; Uríčková and Sádecká, 2015).

To identify crucial information about the quality of the final product during wine fermentation, ultra-performance liquid chromatography (UPLC) coupled with MS/MS analysis and stable isotope dilution assay were proposed (Bonnaffoux et al., 2017; Barnaba et al., 2017). To characterize the bioactive constituents and AA of wines, a rapid, sensitive, and reliable HPLC-DAD-ESI-MS/MS method was proposed, that combined HPLC, photodiode-array detector (DAD), electrospray ionization (ESI), and tandem MS (Lu et al., 2015). Application of an automated multivariate curve resolution technique to nontargeted metabolomic GC-MS analysis of wine makes it possible to detect several hundred volatile compounds within a single analytical run (Schmidtke et al., 2013; de Ovalle et al., 2018).

The potential of vibrational spectroscopy techniques (near infrared, mid-infrared, and Raman) in winemaking has been widely enhanced (Wang et al., 2014; Ilaslan et al., 2015; Mandrile et al., 2016; Chandra et al., 2017; dos Santos et al., 2017). These techniques have accomplished numerous purposes, since the management of soil practices up to the analysis of bottled wine. For monitoring time-related changes in levels of sugar and alcohols (ethanol and glycerol) that occur during wine fermentation, a number of approaches, including autocalibration Fourier transform Raman spectroscopy (FT-RS) and HPLC, was used (Wang et al., 2014). RS was successfully used as a fast effective technique for each of glucose, fructose, and sucrose determination in drinks in comparison with HPLC method (Ilaslan et al., 2015). To evaluate the relationship between the spectra and the concentrations of the tested analytes, principal component analysis (PCA) and partial least-squares approach (PLS) were applied to the RS (Wang et al., 2014; Ilaslan et al., 2015).

Methods of molecular spectroscopy are usually used for estimating wine authenticity and discrimination (Chandra et al., 2017; Mandrile et al., 2016; Waterhouse et al., 2016). Due to the specific chemical fingerprint of the Raman spectrum, it is possible to discriminate different wines fastly in accordance with grape varieties, production area, and aging time (Mandrile et al., 2016). To assess the technique capability for providing direct spectral biomarkers of wines, including alcohol and flavonoids, surface-enhanced Raman scattering technique (SERS) in combination with silver nanoparticles (AgNPs) was applied (Pinzaru and Magdas, 2017). It showed great promise to fast wine monitoring, with substantial advantages over the current traditional approaches.

12.3.4 Microbiological and Genetic Approaches

Wine industry requires enhanced strains to solve commercial and manufacturing problems. Wine yeasts are critical in the winemaking process as they affect several aspects; for example, aroma composition or fermentation. Over the past three decades, consumers have increasingly demanded wine with richer and riper fruit flavor profiles (de Ovalle et al., 2018; Belda et al., 2017; Waterhouse et al., 2016). Thus, wine companies and researchers have attempted to enhance these aspects by different approaches, including genetic modification.

Wine composition is the product of complex interactions among yeast and bacteria that take place in vineyards and wineries, although one yeast species, *Saccharomyces cerevisiae* is the most widespread microorganism responsible for wine alcoholic fermentation. Nevertheless, the wine industry is currently facing new challenges, some of them associate with climate change, which have a negative effect on ethanol content and wine quality. Wine producers are developing and implementing several strategies in the vineyard and winery to reduce the alcohol concentration in wines produced from well-ripened grapes. One approach is to obtain the recombinant *S. cerevisiae* strains by redirecting their carbon metabolism away from ethanol production to other metabolites, such as glycerol. However, this powerful technique has been disused given consumers' rejection of GMOs (Pérez-Torrado et al., 2015).

Numerous and varied strategies have been carried out to overcome these concerns. Several renewed alternative non-GMO techniques were developed and frequently used in recent years to enhance wine yeast, such as adaptive evolution or artificial hybridization (Pérez-Torrado et al., 2015; Zhao et al., 2015; Goold et al., 2017). The use of alternative non-*Saccharomyces* yeasts, yielding lower ethanol concentrations and sometimes giving rise to new and interesting aroma, is one of the trendiest approaches (Belda et al., 2017; Alonso-del-Real

et al., 2017). The combination of different strategies for promoting *Saccharomyces kudriavzevii* prevalence during wine fermentation, such as, co-inoculation with optimal *S. cerevisiae/S. kudriavzevii* proportions together with limited aeration, resulting in an ethanol yield reduction as well as a higher glycerol production (Alonso-del-Real et al., 2017). The potential of another strain—*Torulaspora delbrueckii* on new metabolic features regarding the release of cysteinylated aroma precursors was investigated. Fermentations involving *T. delbrueckii* showed positive contribution to several wine parameters, such as glycerol content, ethanol index, and major volatile compounds composition, but especially on thiols release (Belda et al., 2017). The influence of lactic acid bacteria (LAB) strains on ester levels in Bordeaux red wines was investigated by liquid-liquid-extraction- or HS-SPME-GC/MS at various stages in the winemaking process. The levels of most compounds were shown to be slightly impacted by LAB, depending on grape variety. Nevertheless, branched hydroxylated esters, such as ethyl 2-hydroxy-3-methylbutanoate and ethyl 2-hydroxy-4-methylpentanoate were the only compounds to be strongly influenced by the bacteria strain, regardless of matrix composition or the yeasts used for alcoholic fermentation. These esters are apparently important markers of LAB esterase activity (Gammacurta et al., 2018).

To develop effective strategies for the selection of beneficial bacterial strains and to improve of quality of Hong Qu glutinous rice wine, bacterial flora, present in the traditional fermentation starters, was investigated (Lv et al., 2016) by the method of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry fingerprinting (MALDI-TOF MSF) combined with 16S rRNA gene sequencing and species-specific PCRs. A comparison of 16S rRNA gene phylogeny and MALDI-TOF MS analysis showed that last method was a good complementary approach to 16S rRNA sequencing and even a more powerful tool in the accurate differentiation and classification of *Bacillus* species. MALDI-TOF MSF was found to provide valuable information at species levels for the genus of *Lactobacillus*.

The diversity in demand across global wine markets has increased over the last few years. Traditional wine-producing countries have experienced strong, recent growth in new categories like flavored wines, while new world countries create publicity for such innovations and traditional categories like organic (https://organicwinefind.com) and natural wines (Chan, 2016). The trend in the consumption of organic wines still presents a challenge for the sector, which started in the production of organic grapes for wine processing.

Organics, as an alternative to the traditional system, one combines traditional methods with modern agricultural practices, crop rotation, diversification, better land use, and natural pest control. These practices make organic wine is seen as safe, healthy, and of high quality,

but very difficult for grape growers. The vast majority of organic wine is made from *Vitis vinifera* varieties that are highly susceptible to fungal diseases and pests (Araujoa et al., 2017; Pedneault and Provost, 2016; Provost and Pedneault, 2016). To solve this problem, fungus-resistant grape varieties have been recommended as the most suitable choice in organic viticulture, especially in areas where disease pressure necessitates high rates of fungicides (Pedneault and Provost, 2016).

12.4 The Examples of Wine Analysis With the Use of the Modern Analytical Methods

Scientific investigations on the problems of the search and identification of new fragrances for winemaking, as well as for development of novel methods of dangerous contaminants monitoring, are very actual in last decade. We describe further some examples of recent successful studies concerning this problem.

12.4.1 Volatile Compounds and Antioxidants

The aroma of La Mancha Malbec red wines was characterized by chemical and sensory analysis (Sánchez-Palomo et al., 2017). A total of 79 free volatile compounds were isolated and identified with the use of solid-phase extraction (SPE) and GC-MS as well as quantitative descriptive sensory analysis (QDA). The sensory aroma profile of the tested wines was shown to consist of volatile C_6 and benzene compounds and was characterized by red fruit, fresh, prune, liquorice, clove, caramel, leather, tobacco, and coffee notes. In red wine, the sensory "electronic nose" method distinguishes and identifies up to 800 different volatile compound molecules (García et al., 2006; Ragazzo-Sanchez et al., 2008; Loutfi et al., 2015).

Several analytical approaches, including sensory descriptive analysis associated with GC-olfactometry, have led to the identification of a new terpene, *p*-menth-1-en-3-one (piperitone). Chiral multidimensional GC-mass spectrometry (GC-MS) was used to show that piperitone is present mainly in red wines, at concentrations that do not exceed 435 ng/L (Pons et al., 2016). Another chemical, isolated from organic extracts of musts and red wines, was identified as a fragrant lactone (5,6-dihydro-6-pentyl-2H-pyran-2-one) that corresponds to an odorant zone reminiscent of coconut and dried figs (Pons et al., 2017).

Enantiomers of 2-methylbutyl acetate (MBA) were estimated in red and white commercial wines using chiral gas chromatography (γ-cyclodextrin) and revealed the exclusive presence of the S-enantiomeric form. MBA levels were generally higher in red than in white wines, increasing gradually during aging. Sensory profiles

were highlighted, demonstrating a specific contribution to black-, fresh-, and jammy-fruit notes, despite its subthreshold concentrations (Cameleyre et al., 2017).

Sixty-two volatile compounds were identified in 10 Uruguayan Tannat commercial wines using GC-MS, where the most abundant were alcohols and esters. Sensory characterization of wine aroma was carried out by a panel of wine professionals using projective mapping. Red fruits, fruity, dry fruits, and woody were the main descriptors used to characterize the aroma profile of the wines. Partial least-squares regression (PLSR) enabled explaining many of the most important sensory descriptors (woody, earthy, phenolic, sulfur, chemical, and microbiological) through their volatile composition (Fariña et al., 2015).

Sensory and volatile compositions of Spanish wines were tested by GC-MS and QDA methods. Floral, herbaceous, ripe fruit, and aroma intensity were predicted from volatile data. Relationships between the instrumental (volatile) and sensory variables were analyzed through the application of PLSR. PLSR was demonstrated to be a satisfactory model for predicting aroma descriptors from volatiles (Vilanova et al., 2013).

HPLC method with spectrophotometric and fluorescence modes of detection has revealed up to 48 different phenolic compounds, namely anthocyanins, flavan-3-ols, flavanols, hydroxycinnamate and benzoic acids, and others (Waterhouse et al., 2016).

The study of Brazil wines aroma profiles was performed using spectrophotometry, colorimetry, HPLC, inductively coupled plasma MS, capillary zone electrophoresis, GC, and isotopic ratio MS (Arcari et al., 2013). AA of white and red fortified wines was shown to be correlated significantly ($P < .05$) with the content of total polyphenols, *ortho*-diphenols, tartaric esters, flavonols, total monomeric anthocyanins, total tannins, gallic acid, *trans*-resveratrol, catechin, caffeic acid, coumaric acid, and ferulic acid. The analytical determinations combined with PCA showed the differences in compositions of tested wines according to region of origin, with contributions from the variables AA, the level of organic components (phenols, acids, esters, higher alcohols, etc.), minerals (K^+, Fe^{3+}, Cd^{2+}, Na^+, Ca^{2+}, Co^{2+}, Mg^{2+}), and carbon isotope ratio (Arcari et al., 2013).

The AA of 20 commercial grape juices and 10 typical Spanish wines and their content of total phenolic compounds, anthocyanins, flavonoids, and 10 individual phenolic compounds were measured by HPLC-UV. Red grape juices were shown to have a 1.5-fold higher concentration of total phenols and flavonoids and a 3.5-fold higher AA compared to white grape juices. White grape juices contained more total phenols and flavonoids and evidenced higher AA compared to the white wines. White wines are less effective AA than red wines and contain an eightfold lower content of total phenols and flavonoids (Moreno-Montoro et al., 2015; Lu et al., 2015).

The profiles of simple phenols were characterized in hybrid wines by an online SPE clean-up device combined with ultrahigh liquid chromatography-high-resolution mass spectrometry (UHLC-MS). The phenolic composition of four hybrid grape varieties and two European grape varieties was investigated. A total of 53 free simple phenols and their 79 glycosylated precursors in the forms of hexoside, pentoside, hexoside-hexoside, hexoside-pentoside, entoside-hexoside, and pentoside-pentoside derivatives were identified (Barnaba et al., 2017).

An antioxidant potential of wine was evaluated by electron spin resonance and photometric method by the use of the following free radicals: 2,2-diphenyl-1-picrylhydrazyl, galvinoxyl (2,6-di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadiene-1-ylidene)-*p*-tolyloxy), and hydroxyl. The reducing ability to inactivate free radicals (namely, the reducing of AA of wine) was shown to be the result of the irreversible reaction of metal ions with the polyphenols with formation of inactive complexes (Espinoza et al., 2009).

12.4.2 Unpleasant Contaminants

Heavy metals (toxic Cd, Cu, and Pb) and metalloids (As) were detected by multielement electrothermal atomic adsorption spectrometry (AAS) was used (Argyri et al., 2006), iron compounds—by the molecular absorption spectrometry. The sensitivity of the last method for Fe (II) and Fe (III) are 0.22 and 0.72 μg/L, respectively (Ajtony et al., 2008). Fe, Cu, and Zn are estimated in wines by the methods of flame AAS and electrothermal AAS. To obtain the fractions enriched with the test metals, the organic components of wines (complexes of polyphenols with proteins and polysaccharides) are removed on the XAD-8 sorbent followed by chromatographic fractionation of the cations and metal anions (Ajtony et al., 2008). Cu, Cd, Pb, and Zn in dry wines are quantitatively estimated by the method of anode stripping voltammetry (Ferreira et al., 2007).

Some pollutants in wine samples, in particular Li, Be, Al, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, and As, were tested quantitatively and semiquantitatively using the method of inductively coupled plasma mass spectrometry. The proposed method allows to measure the analyzed compounds (except for Fe and Zn) with a threshold sensitivity of 0.1 μL/L (Karadjova et al., 2002).

Volatile phenols and BA are one of the key molecules responsible for olfactory defects in wine: when their concentrations are greater than the sensory threshold, all wine's organoleptic characteristics might be influenced or damaged. The emergence of these volatile compounds is the result of undesirable microbial activity. BA found in wine were monitored in opened wine bottles kept under different storage conditions, a method of SPE was used prior to analysis by

HPLC (Ordóñez et al., 2017). A lot of BA (methylamine, pyrrolidone, morpholine, isoamylamine, ethylamine, hexylamine, isopropylamine, isobutylamine, *n*-butylamine, *n*-amylamine, dimethylamine, *n*-propylamine, ethanolamine, and 3-methylpropylamine) are formed by the microbial transformation of non-nitrogen compound (Pena-Gallego et al., 2012; Kheir et al., 2013; Nalazek-Rudnicka and Wasik, 2017).

The yeast genus *Brettanomyces* is the only major microorganism that has the ability to produce 4-ethylphenol and 4-ethylguaiacol from hydroxycinnamic acids in red wine (Kheir et al., 2013; Schumaker et al., 2017). Thus, microbiological control (on the absence of *Brettanomyces* in wine) and HPLC analysis (on the level of dangerous ethylphenols) are necessary.

Ethylphenols (2-phenyl ethanol, linalool, and benzaldehyde) was demonstrated to be removed with the timber and sorption by yeast precipitation when the wine is matured in oak barrels for 2 months (Garde-Cerd and Ancin-Azpilicueta, 2006). An investigation conducted on 240 wine samples demonstrated that such "self-purification" of wine with oak wood improves its aroma, color, transparency, and stability, that is, the overall quality of the wine.

For quantitative determination of pesticides, a dispersive method of liquid-liquid microextraction (DLLME), with further fractionation of wine extract by GC-MS approach, was developed and 27 different classes of pesticides were identified in wine, including organochlorine pesticide, organophosphorus pesticide, pyrethroid pesticide, fungicide, herbicide, and acaricide (Chen et al., 2016).

Carcinogenic EC was determined in fermented liquids (red wines, Chinese liquors, and yellow wines) by using ultrahigh-performance liquid chromatography coupled with a Q Exactive hybrid quadrupole-orbitrap mass spectrometer (UHPLC-MS/MS). Good linearity was obtained ($R = 0.9999$) with the limits of detection 1.8 μg/L. The tested beverages were shown to have the normal EC levels—lower than the limits of the Canadian legislation (30 μg/L). The proposed method, being simple in sample preparation without using organic solvents in pretreatment, could be promising for testing EC in fermented liquids (Zhao and Jiang, 2015).

The known physicochemical approaches for monitoring of Arg, as precursor of EC—HPLC, MS, capillary electrophoresis, polarography, and other methods—employ skilled labor techniques, are time consuming and expensive, and often have poor precision, low sensitivity, and selectivity. Different types of biosensors, promising for monitoring Arg (Gayda et al., 2015; Nikolelis and Nikoleli, 2016; Verma et al., 2017b; Dagar and Pundir, 2017; Soldatkin et al., 2017; An et al., 2017) as well as enzymatic-chemical methods (Stasyuk et al., 2013, 2016a,

2017b,c) were proposed. Further development of novel highly selective and sensitive methods for Arg determination is therefore necessary.

12.5 The Development of Analytical Approaches for L-Arginine Determination

12.5.1 Enzymes and Cells

The potential of enzymatic methods, including biosensors, as a means of determining and assuring the quality of wines was clearly illustrated throughout by our previous investigations. We describe in the greater detail enzymatic and biosensor methods for analysis of Arg, as precursor of EC in wine. Enzymes of Arg metabolism [arginase, arginine deiminase (ADI), and arginine decarboxylase] are promising tools for Arg assay (Stasyk et al., 2015). The search for alternative sources for these enzymes, including recombinant microbial cells, as well as the development of effective technologies for enzyme purification and of selective cost-effective analytical methods for Arg assay, is relevant problems.

Some key studies are listed below. We have described and developed the novel enzyme- and cells-based analytical approaches, promising to control Arg level in drinks (fruit juices, wines, and others). In our research, recombinant enzymes as biocatalysts were used. Human liver arginase I (arginase, EC 3.5.3.1) and bacterial ADI (EC 3.5.3.6) were isolated from the cells of recombinant strains *Hansenula polymorpha* and *Escherichia coli*, respectively (Stasyk et al., 2015; Fayura et al., 2013). $(His)_6$-tagged arginase (modified) was purified from the recombinant strain *S. cerevisiae* (Zakalskiy et al., 2012).

12.5.2 Enzymatic Methods

The highly selective and sensitive analytical approaches for the quantitative determination of Arg were elaborated and characterized. These enzymatic-chemical methods are based on the use of recombinant arginase and ADI. Products of enzymatic digestion of Arg, after incubation under special conditions with chemical compounds, 2,3-butanedione monoxime and o-phtalaldehyde, generate colorous, and fluorescence chemicals, which can be quantitatively determined by spectrophotometry and fluorometry).

The principal scheme, that summarizes the proposed enzymatic-chemical methods of Arg determination, is shown in Fig. 12.2.

Analytical characteristics of these methods are demonstrated in Table 12.1.

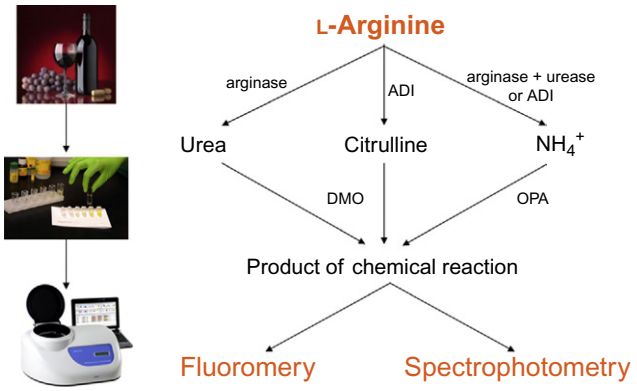

Fig. 12.2 The principal scheme of enzymatic-chemical methods of L-arginine analysis. *DMO*, 2.3-butandione monoxime; *OPA*, o-phtalaldehyde.

All these methods were used for analysis of Arg in real samples of commercial wines.

12.5.3 Electrochemical Biosensors for L-Arginine Determination

The highly selective and sensitive electrochemical biosensors for Arg analysis were proposed. Arginase and ADI, as well as cells of recombinant strain *H. polymorpha*, were used as the bioelements of different biosensors (Table 12.2). The constructed arginase-based

Table 12.1 Analytical Characteristics of the Developed Enzymatic-Chemical Methods of L-Arginine Assay

Method	Enzyme	Linear Range (μM)	Sensitivity (μM)	References
DMO-S	Arginase	7–100	5.0	Stasyuk et al. (2013)
DMO-F	Arginase	0.06–200	0.04	Stasyuk et al. (2013)
OPA-S	Arginase-urease	0.9–60.0	0.85	Stasyuk et al. (2017c)
OPA-F	Arginase-urease	0.09–6.0	0.08	Stasyuk et al. (2017b,c)
OPA-F	ADI	0.35–24	0.25	Stasyuk et al. (2016a, 2017c)
OPA-S	ADI	0.7–50	0.55	Stasyuk et al. (2016a, 2017c)
DMO-S	ADI	4.4–280	2.5	Stasyuk et al. (2017c)
DMO-F	ADI	0.55–140	0.3	Stasyuk et al. (2017c)

DMO, 2.3-butandione monoxime; S, F, spectrophotometric and fluorometric determination of final product, respectively; OPA, o-phtalaldehyde.

Table 12.2 Analytical Characteristics of Electrochemical Biosensors on Arg

Biomembrane	Linearity Range (mM)	Response Time (s) (95%)	Stability, Days (50%)	K_M^{app} (mM)	Sensitivity ($A\,M^{-1}\,m^{-2}$)	References
Arginase/urease	0.07–0.6	10	3	1.27 ± 0.29	110 ± 1.3	Stasyuk et al. (2012)
Arginase/urease	0.12–40	300	13	4.7 ± 0.3	–	Stasyuk et al. (2011)
Arginase-nAu/urease	0.5–50	180	15	1.1 ± 0.2	–	Stasyuk et al. (2011)
p-Cells/urease[a]	Up to 0.6	60	3	0.51 ± 0.05	14 ± 1.2	Stasyuk et al. (2014a)
nAu-enriched p-cells/urease	0.14–1.2	60	3	0.62 ± 0.01	37	Karkovska et al. (2017)
Arginase-nAu-enriched p-cells/urease	0.01–0.7	30	3	0.45 ± 0.09	357	Karkovska et al. (2017)
Arginine deiminase	0.003–0.2	15	Over 35	0.31 ± 0.05	684 ± 32	Zhybak et al. (2017)

[a] This method was used for wine analysis.

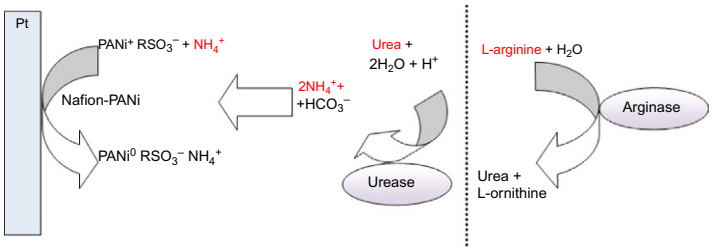

Fig. 12.3 Principal scheme of L-Arg detection by bi-enzyme/PANi-Nafion/Pt-electrode (Stasyuk et al., 2012). PANi+ and PANi—an oxidized and reduced forms of PANi, respectively; RSO_3—a skeleton of Nafion with the sulfonate groups (Luo and Do, 2004).

potentiometric biosensors (Stasyuk et al., 2011), being stable and having the wide linear ranges, has demonstrated rather low sensitivities, due to the limitation by the parameters of physical transducer.

Amperometric biosensors usually have the advantages in the essentially higher sensitivity. The general principle of Arg detection by the bi-enzyme (arginase and urease) amperometric electrode based on NH_4^+ ions sensing was proposed (Fig. 12.3) and optimized by us for the first time (Stasyuk et al., 2012).

The first stage of biorecognition process is enzymatic conversion of Arg to L-ornithine and urea under arginase catalysis or to citrulline and ammonium ions under ADI catalysis. Arginase is not an oxidoreductase, but hydrolase and none of the products being formed in the first reaction are electroactive. The use of urease co-immobilized with arginase (or recombinant cells with elevated level of this enzyme) allows further splitting of urea to ammonium ions being sensed by electroactive polyaniline (PANi)-Nafion membrane placed on Pt electrode according to Luo and Do (2004). The same principle, but in the simpler mono-enzyme variant, without urease, was used in the case of ADI application as biocatalyst (Zhybak et al., 2017). To construct enzyme-based sensor, the biorecognition membrane was fixed on composite electrode with a calcium alginate gel (Stasyuk et al., 2012) or by a cross-linking via glutaraldehyde vapors (Zhybak et al., 2017). To construct cell-based (microbial) sensor, arginase-enriched recombinant intact or permeabilized yeast cells (p-cells) were dropped with urease on the PANi-Nafion/Pt surface and covered with a dialyses membrane (Stasyuk et al., 2014a; Karkovska et al., 2017).

Operational parameters of the bioelectrodes were summarized in Table 12.2. Proposed biosensors are the typical examples of biocatalytic amperometric sensors where a final product of enzymatic reaction interacts with electroactive polymer to induce a change in its current. Under ADI catalysis, Arg was hydrolyzed to citrulline and ammonium ions in one-step reaction. As a result, ADI-based biosensor has significant advantages in comparison with bi-enzyme sensors,

namely, it possesses 12-times higher storage stability and six-times higher sensitivity.

The advantages of nanotechnology were successfully used in biosensors construction. When we compared the constructed cell-based sensors namely (Stasyuk et al., 2014a), with analogous sensor, but enriched with arginase-bound gold nanoparticles (nAu), sensitivity was shown to be 25 times higher and response to analyte two times faster (Karkovska et al., 2017). The enrichment of the cells by the target enzyme was achieved by using nanotechnological approach—transfer of arginase-nAu into the permeabilized yeast cells (Table 12.2). Such effective biosensors may be prospective in laboratories of food industry.

12.5.4 Arginine Analysis in Real Samples of Wine

The works about the application of the created bioanalytical systems for the analysis of biological samples occupy the special place. The developed enzymatic-chemical methods and cell-based biosensor were tested on the samples of commercial wines and juice, some data are presented in Table 12.3, other results are described in detail in our papers (Stasyuk et al., 2013, 2014a, 2016a).

A standard addition test (SAT) was applied to all diluted samples in order to evaluate the possible interference effect of wine components

Table 12.3 Determination of Arg (mM) in the Samples of Drinks by the Developed (Arginase-DMO and Biosensor) and Reference Methods

Samples/Method	Arginase-DMO (Stasyuk et al., 2013)		Chemical (Wang et al., 2008)	Microbial Biosensor (Stasyuk et al., 2014a)
	Spectrophotometric	Fluorometric		
Whiskey Old Smuggler[a]	0.99 ± 0.03	0.85 ± 0.04	0.95 ± 0.02	–
Wine Chardonnay, dry white	0.96 ± 0.05	1.05 ± 0.01	0.97 ± 0.06	0.98 ± 0.11
Wine Mouton Cadet, dry red	1.96 ± 0.04	1.97 ± 0.01	1.95 ± 0.004	1.96 ± 0.05
Wine Soave, dry white[a]	3.80 ± 0.03	3.45 ± 0.05	3.79 ± 0.08	–
Wine Minervois, dry red[a]	0.86 ± 0.02	0.85 ± 0.04	0.89 ± 0.02	–
Wine Bordeaux-2010, dry reda	4.09 ± 0.07	3.80 ± 0.05	3.95 ± 0.09	–
Wine Bastardo, sweet red	2.36 ± 0.06	2.55 ± 0.04	–	2.46 ± 0.06

[a] Unpublished data.

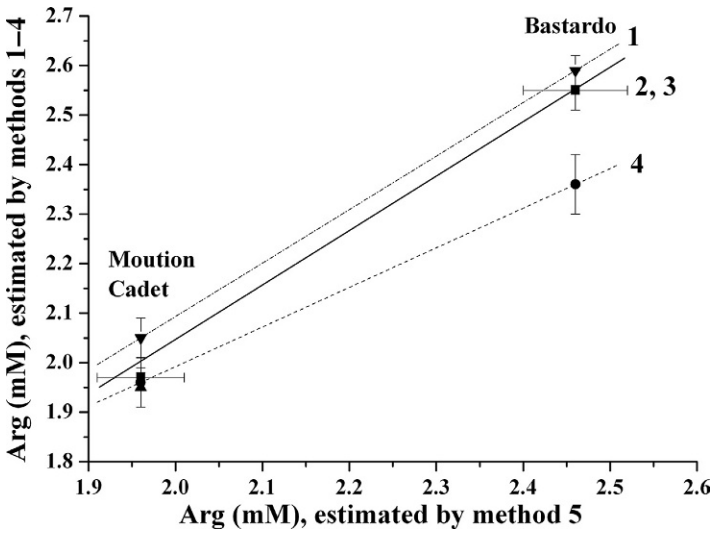

Fig. 12.4 Correlations between the results of Arg analysis in the samples of wines Moution Cadet and Bastardo, estimated by five different methods: (1) fluorometric arginase-DMO, (2) spectrophotometric arginase-DMO, (3) reference chemical, (4) ADI-OPA, and (5) microbial sensor.

on results of Arg estimation. A strong correlation was demonstrated between the Arg values obtained for wine samples using the biosensor, reference standard, and other methods (Fig. 12.4), as well as with the literature data. It is noteworthy that the obtained Arg contents are very similar to those (0–9.5 mM) published by other authors (Austin and Butzke, 2000). Compared with the known standard reference methods, the developed enzymatic systems have a number of significant advantages: a quick time of analysis, a precision measurement, no necessity of the samples pretreatment, high selectivity, and sensitivity.

Hence, the proposed bioanalytical approaches for Arg determination, namely, enzymatic-chemical and biosensor methods, being simple, valid, and low cost, would be promising for quality and safety controls in food industry to predict a potential risk of urethane formation in wine.

12.5.5 Arginase-Based Approaches for Determination of Mn^{2+}

Arginase was shown to be the prospective tool not only for analysis of its own substrate Arg, but also of its own cofactor Mn^{2+}.

The development of simple cost-effective sensitive methods for analysis of toxic metal ions in real samples, including wines, is an actual problem. Metal-dependent enzymes seem to be the promising tools for elaboration of such methods to assay own cofactors. A novel amperometric bi-enzyme biosensor, based on the use of

Mn^{2+}-dependent arginase, was proposed (Stasyuk et al., 2016b). The biosensing layer, consisting of urease and apoenzyme of arginase (apo-agrinase), was placed onto a polyaniline-Nafion composite platinum electrode. The principal scheme of Mn^{2+}-sensitive biosensor is similar to those, presented in Fig. 12.3.

Binding of Mn^{2+} with the immobilized on electrode apo-arginase induces reconstruction of the holoenzyme (holo-arginase) followed by generation of ammonium ions from Arg in arginase-urease catalyzed reactions. The resulting NH_4^+ ions diffuse further to the PANi-Nafion film and trigger the reduction of PANi on the Pt electrode. The last product is monitored at the working potential of −200 mV.

The resulted sensor revealed a high sensitivity to Mn^{2+} ions approximately 9200 ± 20 A/(Mm^2) with the apparent Michaelis-Menten constant derived from Mn^{2+} ions calibration curve of 11.5 ± 1.0 μM. A linear concentration range was observed from 1 to 6.5 μM $MnCl_2$, a limit of detection being of 0.15 μM and a response time is 2.5 min. The proposed biosensor may be useful to monitor manganese compounds in laboratories of food industry and environmental control service.

Another novel approach, based on the apoenzyme of arginase, is enzymatic-chemical method for assay of manganese (II) and cobalt (II) ions. The metal ion content in the tested samples can be determined by measuring the level of urea generated after enzymatic hydrolysis of Arg by reconstructed arginase holoenzyme in the presence of tested metal ions. This highly sensitive, selective, valid, and low-cost method may be useful for monitoring the content of target ions in food industry, including in winemaking, due to the high stability of apo-arginase (Stasyuk et al., 2018).

12.6 Biosensor Methods for Analysis of Mandatory Components of Wine

12.6.1 Biocatalysts

In our previous research, a variety of selected or genetic-engineering microbial cells, overproducers of analytically important enzymes, was obtained (Gonchar et al., 1990; Smutok et al., 2007; Zakalskiy et al., 2012; Sigawi et al., 2014; Stasyk et al., 2015) and the target enzymes were isolated by us from the correspondent cells. Highly purified yeast alcohol oxidase (AO) was isolated from the selected yeast *H. polymorpha* C-105 (*gcr1 catX*) (Gonchar et al., 1990; Shleev et al., 2006), mutated forms of AO, with several point mutations in the *AOX* gene, were purified from the correspondent strains of *H. polymorpha* CA2 and CA4 (Dmytruk et al., 2007).

Thermostable yeast L-lactate:cytochrome *c*-oxidoreductase (EC 1.1.2.3, flavocytochrome b_2, FC b_2) was isolated from the cells *H. polymorpha 356* (Gaida et al., 2003; Smutok et al., 2006a, 2011) and from the gene-engineered overproducing strain **tr1**, constructed on the base of strain *H. polymorpha* C-105 by overexpression of the gene *CYB2 H. polymorpha* encoding target enzyme (Smutok et al., 2007). The constructed strain **tr1** is thermotolerant and able to produce a six- to eightfold higher quantity of enzyme when compared to the parental strain.

Glycerol oxidase (GlO) was isolated from the cells of fungus *Botrytis allii* (Gayda et al., 2006; Goriushkina et al., 2010), NAD^+-dependent glycerol dehydrogenase (GDH)—from the recombinant yeast *S. cerevisiae W303* (*HpGDH*) (Synenka et al., 2015). GOx *Penicillium adametzii* was produced in Institute of Microbiology, Minsk, Belarus.

The listed enzymes and/or their parental microbial cells were used as biocatalysts for the development of amperometric biosensors for monitoring key components of wine, including L-lactate, ethanol, glucose, and glycerol, which are usually tested in every wine. Analytical characteristics of the developed biosensors are demonstrated in Tables 12.4–12.6.

12.6.2 Biosensors on L-Lactate

Reliable determination of L-lactate is important in food technology, fermentation, and wine industries. Enzyme- and cell-based amperometric biosensors look very promising due to the favorable coupling of the selectivity of the biological recognition element and the sensitivity of electrochemical transducer. A number of amperometric L-lactate-selective biosensors were developed with Fcb_2 and its parental yeast cells (Table 12.4).

The first Fcb_2-based amperometric biosensor to L-lactate has been developed using enzyme isolated for the first time from thermotolerant methylotrophic yeast *H. polymorpha 356* (Smutok et al., 2005, 2006a). Different immobilization methods and low-molecular free-diffusing redox mediators have been tested for optimizing the electrochemical communication between the immobilized enzyme and the electrode surface. Moreover, the possibility of direct electron transfer from the reduced form of Fcb_2 to carbon electrodes (CEs) has been evaluated. The bioanalytical properties of Fcb_2-based biosensors, such as signal rise time, dynamic range, dependence of the sensor output on the pH value, the temperature, and the storage stability were investigated, and the proposed biosensor demonstrated a very fast response and a high selectivity for L-lactate determination (Smutok et al., 2005, 2006a). The proposed biosensor was successfully tested in the samples of

Table 12.4 Analytical Characteristics of L-Lactate-Selective Biosensors

Biomembrane	Linearity Range (mM)	Response Time (s) (95%)	Stability, Days (50%)	K_M^{app} (mM)	Sensitivity ($A \cdot M^{-1} \cdot m^{-2}$)	References
FC b_2 free with redox mediator[a]	Up to 0.5 Up to 1	6	7	0.52 ± 0.02 1.00 ± 0.02	–	Smutok et al. (2005, 2006a)
FC b_2 free	Up to 0.5	30	–	0.94 ± 0.24	11.0	
FC b_2-nAu without redox mediator	0.3–2.0	20	34	$0.79 \pm 0.0\,3$	106	Karkovska et al. (2015)
p-Cells of recombinant yeast tr1 (rp-cells)	Up to 1.6	20	Over 40	8.0 ± 0.66	–	Smutok et al. (2007)
Intact yeast cells	0.3–2.7	60	–	–	4.1	Karkovska et al. (2017)
Permeabilized yeast cells (p-cells)	0.3–2.7	30	–	–	18.7	Karkovska et al. (2017)
FC b_2-nAu-enriched p-cells	0.3–2.7	5	–	–	48.6	Karkovska et al. (2015)

[a] This method was used for wine analysis.

commercial wines for L-lactate analysis (Table 12.6). But this biosensor was not sufficiently stable.

Thus, the improved biosensors were developed with the use of recombinant Fcb_2 and correspondent parental yeast cells (Smutok et al., 2007). The Fcb_2, being located in the intermembrane space of mitochondria, hence is not easily accessible for redox mediators. After cells permeabilization, free-diffusing mediators can effectively diffuse into the p-cells and interact with Fcb_2, causing efficient oxidation of L-lactate and arising of electric signal on amperometric electrode. The proposed biosensor, being very stable, exhibited a higher K_M^{app} value and hence expanded linear range toward L-lactate as compared to a similar sensor based on the parental yeast cells (Table 12.4).

For further improving of microbial sensor parameters, the enrichment of the sensing cells by the target enzyme was achieved by a combination of genetic and original nanotechnology approaches, namely, by overexpression the corresponding *HpCYB2* gene in the recombinant cells and by the transfer of enzyme-bound gold nanoparticles (Fcb_2-nAu) into the cells (Karkovska et al., 2015, 2017).

Table 12.5 Analytical Characteristics of Ethanol-Sensitive Biosensors, Based on Alcohol Oxidase (AO)

Biomembrane	Linearity Range (mM)	Response Time (s) (95%)	Stability, Days (50%)	K_M^{app} (mM)	Sensitivity ($A\,M^{-1}\,m^{-2}$)	References
AO/peroxidase (AO/HRP)[a]	Up to 1.8	45	16	1.94 ± 0.37	29	Smutok et al. (2006b)
Mutated AO/HRP	Up to 4.0	–	14	5.4 ± 0.8	–	Dmytruk et al. (2007)
AO-nAu-enriched permeabilized yeast cells (p-cells)	Up to 2.0	20	30	1.93 ± 0.08	–	Karkovska et al. (2017)
AO/HRP-like nanozyme	0.01–0.25	15	12	1.99 ± 0.08	357 ± 35	Stasyuk et al. (2019)

[a] This method was used for wine analysis.

Table 12.6 The Results of L-Lactate and Ethanol Determination in the Samples of Wines by Means of the Different Methods

Analyte Method	L-Lactate Content (g/L)				Ethanol Content (V/V, %)		
	FC b_2-Based Methods						
	Biosensor	Formazane	Prussian Blue	IEC	AO-Biosensor	GLC	Alcotest
Wine samples							
Cabernet Sauvignon, red dry	2.4 ± 0.28	2.15 ± 0.13	2.25 ± 0.18	2.5 ± 0.2	12.5 ± 1.4	11.4	10.8 ± 1.6
Chardonnay, white dry	1.16 ± 0.11	0.97 ± 0.12	1.03 ± 0.08	3.0 ± 0.2	10.6 ± 0.4	10.9	10.8 ± 1.1
Sherry Strong, sweet	0.58 ± 0.05	0.49 ± 0.08	0.6 ± 0.07	1.1 ± 0.2	16.8 ± 0.9	18.6	18.2 ± 4.3
References	Smutok et al. (2006a)	Smutok et al. (2013)	Gonchar et al. (2009)	Smutok et al. (2006a)	Smutok et al. (2006b)		

IC, ion-exchange chromatography coupled with colorimetry; *GLC*, gas-liquid chromatography.

The resulted biosensors were shown to possess the high sensitivity and the fast response.

To achieve the excellent characteristics of enzyme-based sensor, the use of gold electrode, modified by Fcb_2-nAu cluster was proposed recently (Karkovska et al., 2015). This biosensor was shown to demonstrate ninefold higher sensitivity to L-lactate and wider linear range in comparison with the characteristics for free enzyme, immobilized on the same electrode (Table 12.4).

12.6.3 Biosensors on Ethanol

A highly stable and sensitive amperometric ethanol biosensors were developed using AO isolated from thermotolerant methylotrophic yeast *H. polymorpha* as biorecognition elements (Smutok et al., 2006b; Shkotova et al., 2006).

To construct bi-enzyme sensor, immobilization of AO was performed by means of electrodeposition paints (EDPs) with a first-layer integrating and HRP within an Os-complex modified EDP (Smutok et al., 2006a). Mono-enzyme AO-based biosensor was developed by electrochemical deposition of the Resydrol polymer, conjugated with AO, under experimentally chosen optimal conditions. The biosensors developed show good analytical characteristics such as reproducibility, operational, and storage stability. The minimal detection limit was 3.5×10^{-2} (% v/v) of ethanol. The biosensor developed has been shown to be a potential for ethanol detection in real alcoholic beverages (Shkotova et al., 2006). Electroactive polymers were used in both variants of sensors in order to assure fast electron transfer between the enzyme and the electrode surface.

With the aim to optimize the electrochemical communication between the immobilized enzymes and the electrode surface, a variety of sensor architectures were investigated. Bioanalytical properties of the most effective AO/HRP-based alcohol biosensor, such as response time, dynamic range for different analytes (primary alcohols and formaldehyde), operational, and storage stability, were investigated (Table 12.5). The best biosensor with architecture *HRP/Os-Ap59//AOX/CP9* was applied for the determination of ethanol in wine samples (Table 12.6).

Other variants of biosensors on ethanol were investigated. As bio-recognition elements, mutated forms of AO, co-immobilized with HRP on electrode (Dmytruk et al., 2007) and permeabilized yeast cells, enriched by AO-nAu, were employed (Karkovska et al., 2017). The most effective mono-enzyme AO-based biosensor on ethanol was constructed with the use of peroxidase-like NPs (Table 12.5). This biosensor, being rather stable and very sensitive, was successfully tested on the several real samples of wines (Stasyuk et al., 2019).

An effectiveness of the developed amperometric biosensors for assay of L-lactate and ethanol was demonstrated on the real samples of commercial wines (Table 12.6). For assay of L-lactate content in real wine samples, the developed "bilayer" biosensor has been tested (Smutok et al., 2006a). The ethanol content in wine samples was determined by means of amperometry at constant potential (−50 mV) using the developed bi-enzyme sensors as working electrodes (Smutok et al., 2006b). The stable wine samples received from *Magarach* winery (the Crimea, Ukraine) were taken for experiments. The method of standard additions has been used for analysis of analytes in wine samples.

The concentrations of L-lactate for diluted samples of wines *Cabernet Sauvignon*, *Chardonnay*, and *Sherry Strong* have been calculated by extrapolation. The best correlation between the values obtained by the new biosensor and the method used in wineries was observed for red wine *Cabernet Sauvignon* and good correlation for all wines was revealed between the biosensor and the enzymatic-chemical methods developed by us (Table 12.6). Significant difference between the results obtained by the developed biosensor and by the traditional method for two wines can be explained by low precision of the latter method.

The main advantage of the developed enzyme-based biosensors, for L-lactate and ethanol assay, is a simple procedure of sample's preparation: no sample pretreatment or derivatization was applied other than a dilution in buffer. The proposed approaches, both biosensors and enzymatic-chemical methods, were shown to be prospective in the future for wine quality control.

12.6.4 Biosensors on Glucose, Glycerol, and Biogenic Amines

Glucose-selective biosensors were developed using microbial GOx and HRP conjugated with NPs of noble metals: AgNPs, Au/AgNPs, and Ag/AuNPs. Co-immobilized enzymes as bioelements (bio) were placed on the surface of CEs. The electrochemical performances of the resulted NPs-modified bioelectrodes (bioNPs/CE) were studied by cyclic voltamperometry and chronoamperometry in comparison with unmodified HRP-GOx-based bioelectrode (bio/CE). The HRP and GOx immobilized on the surface of NPs exhibited an excellent electrocatalytic response toward reduction of glucose at a rather low potential (−50 mV). All developed bioNPs/CEs showed the higher sensitivities, wider linear ranges, lower limits of detection, and higher stabilities in comparison with bio/CE. The most effective bioAgNPs/CE biosensor was used for glucose analysis in the sample of wines. A high correlation with the glucose values estimated by biosensor and commercial enzymatic kit was demonstrated (Stasyuk et al., 2017a).

An amperometric biosensor for glycerol determination was developed using fungal GlO (Goriushkina et al., 2010). Electrochemical polymerization in polymer poly(3,4-thylenedioxythiophene) has been chosen as the most effective method of GlO immobilization on the surface of SensLab printed platinum electrode. The developed glycerol biosensor is characterized by wide linear range and low detection limit of 0.05 mM glycerol, storage stability at the 75% activity level in 15 days after immobilization into sensitive membrane.

Other variants of biosensors on glycerol, based on recombinant yeast GDH (Synenka et al., 2015) and permeabilized fungi cells/HRP (Demkiv et al., 2016), were proposed recently. Analytical characteristics of the fabricated prototypes of biosensors are summarized in Table 12.6. Several enzymatic-chemical methods for glycerol determination, based on the use of GDH, were developed and successfully tested on the samples of commercial wines.

A novel methylamine-selective amperometric bienzyme biosensors based on recombinant primary $(His)_6$-tagged yeast amine oxidase (AMO) isolated from the recombinant yeast strain *S. cerevisiae* and commercial HRP were developed (Sigawi et al., 2014; Stasyuk et al., 2014b). Two AMO preparations were used: free enzyme (AMO) and covalently immobilized on the surface of gold nanoparticles (AMO-nAu). The proposed biosensors, being rather stable, demonstrated a good selectivity toward methylamine (MA): signal for dimethylamine and trimethylamine is <5% and for ethylamine 15% compared to MA output. The constructed biosensor was used for MA assay in real samples of food products in comparison with the chemical method. The values obtained with using both approaches demonstrated a high correlation.

In Table 12.7 some bioanalytical parameters of the developed amperometric biosensors on glucose, glycerol, and BA were presented.

The developed laboratory prototypes of the enzymatic and microbial biosensors were tested on real food samples (data not shown). The described biosensors, in the case of their improving, careful study, and accurate testing on real samples of wines and successful correlation of the obtained results with data, obtained by using referent standard methods, could be recommended to control wine quality.

12.6.5 Trends and Prospects in Biosensors Construction

Last years, nanotechnology is the most developing branch due to a wide variety of potential applications, including the development of novel biosensors, which can be applicable in enology. The unique optical, electrical, and electrochemical properties of the nanomaterials provide novel interesting alternatives to conventional platforms for

Table 12.7 Analytical Characteristics of the Developed Biosensors on D-Glucose, L-Lactate, and MA

Analyte	Biomembrane	Linearity Range (mM)	Response Time (s) (95%)	Stability, days (50%)	K_M^{app} (mM)	Sensitivity ($A\,M^{-1}\,m^{-2}$)	References
Glucose	Glucose oxidase/ HRP (GOx/HRP)	0.5–2.5	20	7	1.5	3.5 ± 0.5	Stasyuk et al. (2017a)
Glucose[a]	GOx/HRPnAg	0.02–1.2	20	12	1.15	113.5 ± 6.2	Stasyuk et al. (2017a)
Glycerol	Glycerol oxidase (GIO)	0.05–25.6	–	15	–	–	Goriushkina et al. (2010)
Glycerol	Permeabilized cells (p-cells)/HRP	Up to 10	30	7	19.93 ± 4.16	–	Demkiv et al. (2016)
Glycerol[a]	Glycerol dehydrogenase	Up to 8	20	2	2.53 ± 0.20	–	Synenka et al. (2015)
Methyl amine	AMO/HRP	15–60	10	7	0.039 ± 0.003	1450 ± 113	Stasyuk et al. (2014b)
	AMO-nAu/HRP	15–150	20	16	0.15 ± 0.03	700 ± 30	

[a] This method was used for wine analysis.

biosensor development, with improved stability, sensitivity, selectivity, and indirect detection (Gonchar et al., 2017; Verma et al., 2017b).

Combining nanobiotechnology with electrochemical biosensors (enzyme or cell-based) has become a crucially novel strategy for the development of simple and reliable monitoring systems for food quality and safety. Nanomaterials also endow electrochemical biosensors with device miniaturization and high sensitivity and specificity. They therefore have great potential for on-site food safety assessment (Nikolelis and Nikoleli, 2016; Gonchar et al., 2017).

One of the most studied opportunities for NPs in enology is their use as constituents of sensors for analyzing wine components like polyphenols, BA, ochratoxin A (Morata et al., 2016) as well as pesticides, veterinary drug residues, additives, inorganic and organic contaminants, pathogens, and toxins (Zeng et al., 2016). There are many advantages with incorporating such materials in the detector device, among them, NPs provide an improvement in the electrochemical properties of the electrodes, thus making the detection more sensible, accurate, selective, with lower limits of detection, wider ranges of linear response, and shorter response times. The NPs conjugated with various biological molecules or cells are attractive candidates for using as the biocatalytic elements with improved sensing characteristics in sensor technologies (Morata et al., 2016; Zeng et al., 2016; Gonchar et al., 2017; Gayda et al., 2019).

Although, the high permeability of the intact cells to NPs is being intensively studied, the idea of using both recombinant technology and nanotechnology to increase the amount of the target enzyme in the biosensing layer is really novel (Karkovska et al., 2015, 2017).

Catalytically active nanomaterials (nanozymes) as artificial enzymes have several advantages over natural analogues, namely, a high stability and low cost. Enzyme-like nanozymes, including metallic nanocomposites, are promising catalysts for biosensing applications (Stasyuk et al., 2019). Peroxidase-liked nanozymes may be as efficient chemosensors on hydrogen peroxide, final product of oxidase-catalyzed hydrolysis of oxidase's substrate. Therefore, selection and development of artificial enzymes are actual tasks of nanotechnology (Lin et al., 2014).

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