Chapter

Improvement of the Bioactive Profile in Wines and Its Incidence on Human Health: Technological Strategies

Ricardo Vejarano, Angie Gil-Calderón, Valeria Díaz-Silva and Jackeline León-Vargas

Abstract

The current lifestyle and the greater awareness of the health benefits of wine are causing an increase in demand for wines with higher levels of bioactive compounds, principally red wine. Scientific evidence supports the benefits of wine, mainly related to their antioxidant and anti-inflammatory activities. This chapter, in its first section, reviews previous studies aiming to elucidate the action mechanisms through which the bioactive compounds act on the human organism in the prevention of diseases. According to the existing literature, studies dealing with specific procedures to enhance the bioactive profile of wines are scarce. Therefore, in the second section, we pay attention to some aspects related with applicable technological strategies during the winemaking process and its incidence in the extraction and stability of bioactive compounds. Furthermore, we discuss some applicable strategies in (i) the vineyard during the vine cultivation and (ii) the raw material level in pre-fermentative stage within winery, as well as, biotechnological strategies during the fermentation and aging. All these are directed to improve the content of bioactive compounds in the wine and, thus, transmit its benefits to the consumer's health.

Keywords: wine, bioactive compounds, bioactive compounds extraction, disease prevention

1. Introduction

It is known that the content of bioactive compounds is greater in red wines, so that more health benefits can be expected by its consumption. This is the reason most studies are conducted on these wines.

Among the most studied compounds are the anthocyanins, which can be found in the skin and represent between 50 and 60% of the phenolic fraction in the red grapes (dry weight basis) [1]. For its part, the flavanols are mainly found in grape seeds with predominance of catechin over its isomer epicatechin [2], while the tannins are mostly grouped in procyanidins (catechin and epicatechin derivatives) and prodelphinidins (derived from gallocatechin and epigallocatechin) [3]. Other important groups are the stilbenes, mainly resveratrol, to which much of the protective effects of wine are attributed. Also, flavonols such as quercetin, myricetin, and kaempferol, predominant in *Vitis vinifera*, are also worth mentioning.

2. Health benefits of wine

2.1 Antioxidant activity

This activity is perhaps the most important concerning the prevention of diseases, due to the presence of phenolic compounds. Among the most important action mechanisms, the prevention of oxidative damage caused by free radicals stands out. This mechanism relies on the capture of unpaired electrons and generation of less reactive species, as well as well as the chelation of metal-ions such as Fe or Cu, to avoid the production of new free radicals [4, 5]. Other mechanisms include the interruption of self-oxidation chain reactions, deactivation of singlet oxygen, suppression of nitrosative stress, synergy with other antioxidants, activation of antioxidant enzymes, and inhibition of oxidant enzymes [6], among others.

The antioxidant efficacy would be determined by the chemical nature. For instance, the anthocyanin B-ring substitution rate is crucial due to its potential to neutralize free radicals [7], mostly in the malvidin, since it contains two methoxyl groups (-OCH_3) and one hydroxyl (-OH) group in the B-ring.

Similar behavior has been observed in gallotannins (epicatechin gallate and epigallocatechin gallate) arising from high concentration of OH groups with higher antioxidant activity than the non-gallates (catechin and epicatechin) [8]. Moreover, the antioxidant activity might improve with the synergistic tannin-tannin interaction [8] or between tannins and other compounds such as quercetin and resveratrol, reducing the lipid peroxidation caused by physical activity, for instance, in athletes [9].

The resveratrol is one of the compounds with the most antioxidant activity as it shows anti-aging activity due to its stimulant action on sirtuins [10]. Also, it is able to suppress free radical production, regulate the antioxidant enzymes activity, and induce endogenous antioxidant defenses such as Nrf2 [nuclear factor (erythroid-derived 2)-like 2] pathway [11], which regulates the expression of inflammatory markers, protecting against diseases such as Parkinson's [12].

The quercetin also contributes to reduce oxidative stress acting on the anion O_2- and over the enzymes that produce it [13].

Also, the benefits of alcohol-free red wine have been observed, which include activity increase of SOD, catalase, and glutathione reductase enzymes [14] and the production of nitric oxide (NO) [15]. The latter is closely related to a lower cardiovascular risk [16].

2.2 Anti-inflammatory activity

Inflammation is a natural bodily response against the presence of injuries or harmful agents. Among these agents, free radicals can activate the production of pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α) [17], which in turn can lead to increased oxidative stress in a cycle that contributes to the progression of many diseases.

Anti-inflammatory compounds, such as resveratrol, have been proven to be effective against cyclooxygenase (COX) enzyme, which is involved in the production of prostaglandins that stimulate the growth of tumor cells [18]; in addition, resveratrol enhances the insulin sensitivity in diabetic patients by the activation of sirtuins, which are responsible for inhibiting inflammatory processes and the secretion of TNFα factor [19, 20]. Also, resveratrol acts on microglia, involved in the defense of an injury or disease of central nervous system (CNS) [21]. Thus, the inhibition of microglial activation may help prevent several disorders. Besides, resveratrol also presents protective activity against cardiovascular diseases (CVD), by inhibiting TNFα and interleukin 6 (IL-6) [22].

Specific cases related to some pathologies are discussed in detail below.

2.3 Protection against cardiovascular diseases

There is vast evidence linking the moderate consumption of wine to lower CVD predominance, with the reports by Renaud and de Logeril [23] and St. Leger et al. [24] being pioneers in the study of the known French paradox. These studies explained the lower incidence of CVD in France despite the high consumption of saturated fats. Later studies have shown the benefits for cardiovascular risk biomarkers (**Figure 1**), which are mainly attributed to phenolic compounds.

Also, the presence of ethanol has been associated with low-density lipoprotein (LDL) and triglycerides level reduction and with the increase of high-density lipoprotein (HDL) at doses of 15–30 grams of ethanol per day [26]. Later studies suggest that moderate ethanol ingestion can increase HDL levels, apolipoprotein A1 (ApoA1) and adiponectin, in addition to lowering fibrinogen levels [27]. Nonetheless, such results suggest the need for further studies due to negative effects of excessive ingestion of ethanol.

Other compounds coming from grapes, such as melatonin and phytosterols (β-sitosterol, stigmasterol, and campesterol), have also shown protective effects against CVD either individually or in synergy with phenols [28]. Melatonin has shown effects against clinic indicators such as blood pressure, NO metabolism, and endothelial functions [29, 30] in addition to the effects on free radicals [31].

Moreover, β-sitosterol, stigmasterol, and campesterol have shown hypocholesterolemic effects by reducing the plasmatic levels of LDL (up to 10%), LDL/HDL ratio (up to 11.5%), and intestinal absorption of cholesterol (30–40%) [32–34].

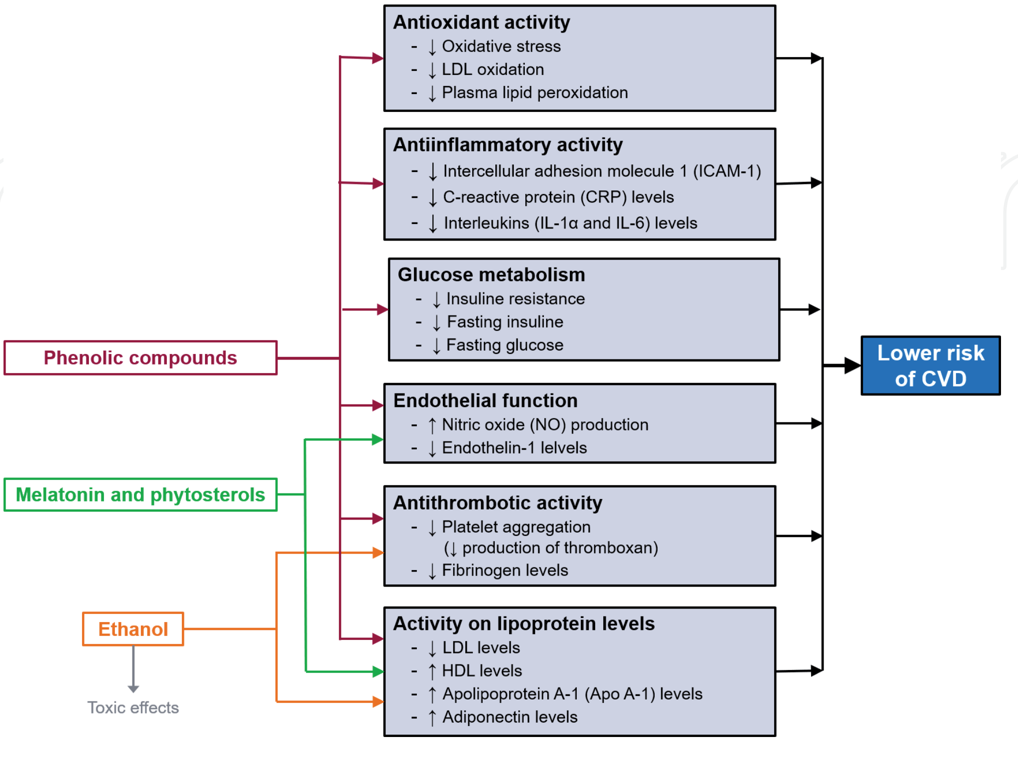

Figure 1.
Effects of wine components for cardiovascular risk factors. Adapted from Ref. [25].

2.4 Neuroprotective effects

2.4.1 Prevention of memory loss

Wine consumption could reduce the memory loss caused by cerebral circulatory insufficiency by increasing the acetylcholine levels, proteins responsible for the organization of brain cells [36], and the prevention of platelet aggregation by ethanol [37]. Other mechanisms include the resveratrol action on the telomerase enzyme, involved in preventing cell senescence and delayed cognitive impairment [38], or the action of the quercetin against cell aging by means of the activation of proteasome complex [39].

2.4.2 Action against cerebrovascular infarctions

In the Copenhagen City Heart Study, it was observed that participants who consumed wine moderately had 50% less risk of dying from cerebral infarction [40] due to the enhancement of the cerebral blood flow, the effect mainly attributed to resveratrol.

In addition, resveratrol interacts with estrogen receptors α and β, reducing cholesterol levels and the formation of atherosclerotic plaque and therefore the risk of stroke due to circulatory failure, for example, in postmenopausal women [41]. Resveratrol has also been shown neuroprotective activity against inflammatory mediators, such as interleukin 1β (IL-1β) and TNF-α, as well as keeping the levels of proteins occludin and claudin-5, of vital importance for the permeability and tissue integrity [42], and to attenuate the cellular apoptosis in ischemia-reperfusion injuries [43], which diminish cell death and the development of diseases such as Alzheimer's.

2.4.3 Antidepressant effect

This effect has been studied in rodents by administration of resveratrol, which can regulate the monoaminergic system, increasing the levels of serotonin, noradrenaline, and dopamine [44]. Also, resveratrol, quercetin, ferulic acid, ellagic acid, and proanthocyanidins can modulate the hypothalamic-pituitary-adrenal (HPA) axis activity as well as the serotonergic neurotransmission [45, 46], which are important mechanisms against anxiety and depression.

2.5 Anticarcinogenic activity

Cancer development comprises the following stages: initiation, promotion, progression, invasion, and metastasis (**Figure 2**). Initiation corresponds to DNA damage by free radicals, inflammatory mediators, cigarette smoke, radiation, etc. [47–49], which may induce genetic mutation and reproduction of mutated cells giving rise to carcinogenesis.

Greater protective effect has been observed with phenolic compounds, for example, apoptotic activity of ellagic acid [50] and delphinidin [51] in colon cancer cells. Delphinidin has also shown activity in leukemia, liver [52], and prostate cancer cells [53]. Resveratrol can also induce cell apoptosis [54].

For its part, proanthocyanidins can alter the migration and invasion processes in human pancreatic cancer [55]. Delphinidin and cyanidin has proven their antimetastatic activity in human colon cancer cells [56], while resveratrol has the same effect on lung cancer cells [57]. More specific mechanisms are shown in **Figure 2**.

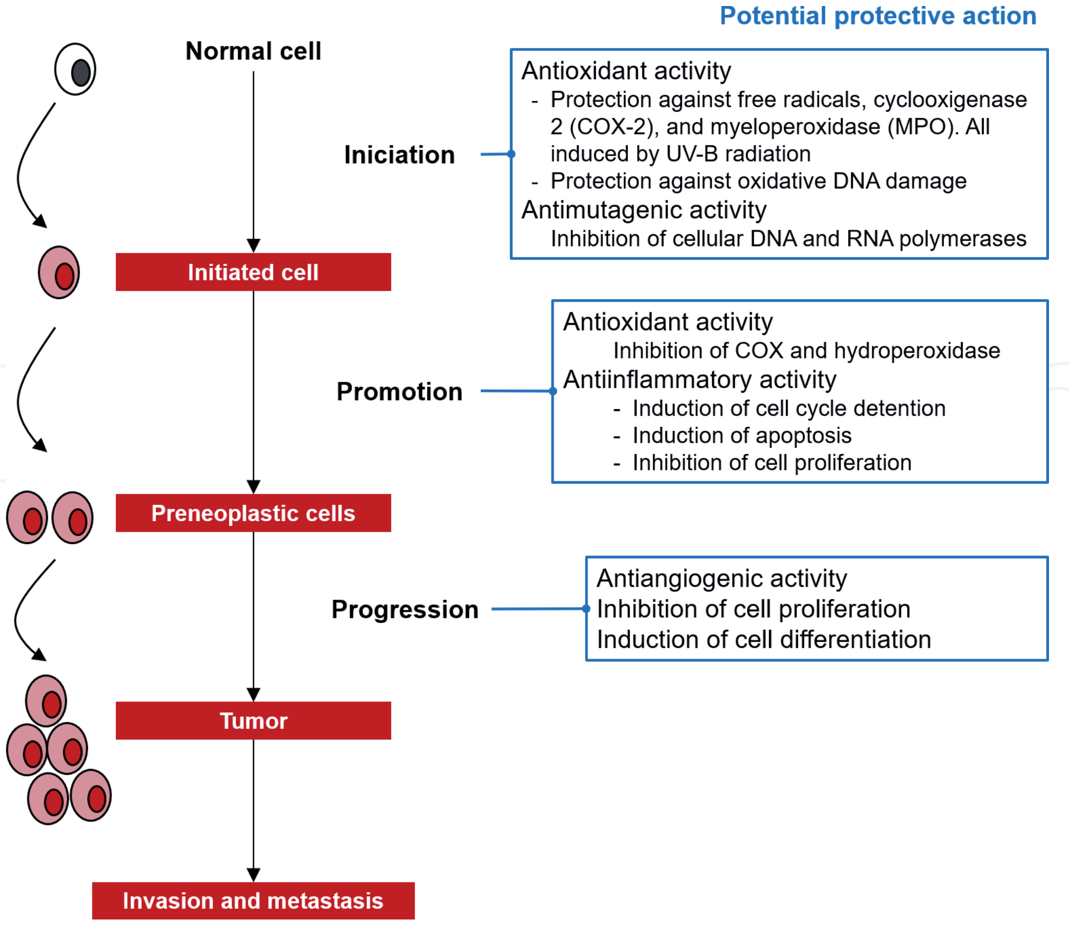

Figure 2.
Potential protective mechanisms of the phenolic compounds at different cancer stages. Adapted from Ref. [35].

2.6 Antimicrobial and antiviral activities

Red wine presents activity against *Streptococcus mutans*, *Streptococcus oralis*, *Fusobacterium nucleatum*, and *Actinomyces oris* implicated in the formation of dental cavities and periodontitis [58], in addition to *Clostridium* [59], *Candida albicans*, and *Botrytis cinerea* [60], among other microorganisms.

White wine also presents activity against *Salmonella* [61]. However, the authors argued that the effect may be associated with the presence of malic acid, since the white wine is not subjected to malolactic fermentation.

Besides, wine's activity is also effective against some viruses, which include human immunodeficiency virus (HIV) [62], hepatitis virus and adenovirus (respiratory infections), cytomegalovirus (chickenpox and infectious mononucleosis), and norovirus and rotavirus (gastroenteritis) [60].

Nonetheless, it is worth mentioning that the antimicrobial and antiviral activities showed by the wine and/or their components cannot be compared to the one attributed to antibiotics. Therefore, wine should not be used for such purposes.

3. Enhancement of bioactive compounds content

3.1 Vineyard: synthesis of bioactive compounds

The wine composition is closely related with the grape composition that mainly depends on its variety. Some compounds, such as resveratrol can reach concentrations of up to 6 mg L^{-1} in wines made of Pinot noir grapes [63], quercetin, concentrations of up to 13 mg L^{-1} in wines made of Shiraz grapes [64], or β-sitosterol, up to 106 mg/100 g of dry skin in Groppello grapes [65].

Other factors which may also induce a better synthesis of bioactive compounds at the vineyard stage are the cultivation conditions and viticulture practices (**Figure 3**). Some examples include the increase in anthocyanin and tannin levels by exposing grape bunches to sunlight and UV radiation [66], which resembles the effect observed in quercetin [67] and resveratrol [68]. In addition, agrochemical elicitation may induce the synthesis of resveratrol [69], melatonin [70], β-sitosterol, and other sterols [65].

However, conditions, such as high temperatures, can slow down the synthesis of phenolic compound, mainly anthocyanins, promoting the synthesis and accumulation of sugars in berries [71] and affecting the levels of extractable bioactive compounds during winemaking process.

3.2 Pre-fermentation treatments

Although most of the procedures are intended to enhance the physicochemical stability and sensory profile, these can be advantageous to improve the bioactive profile of wine, considering that 50% of these compounds are extracted during the winemaking process [64].

The contact time between skins and grape-must/wine can affect the content of compounds such as resveratrol, whose maximum extraction can be realized after 10 days of contact [72]. Also, the use of pre-fermentation enzymes and cold maceration can assist in the extraction of anthocyanins and tannins [73].

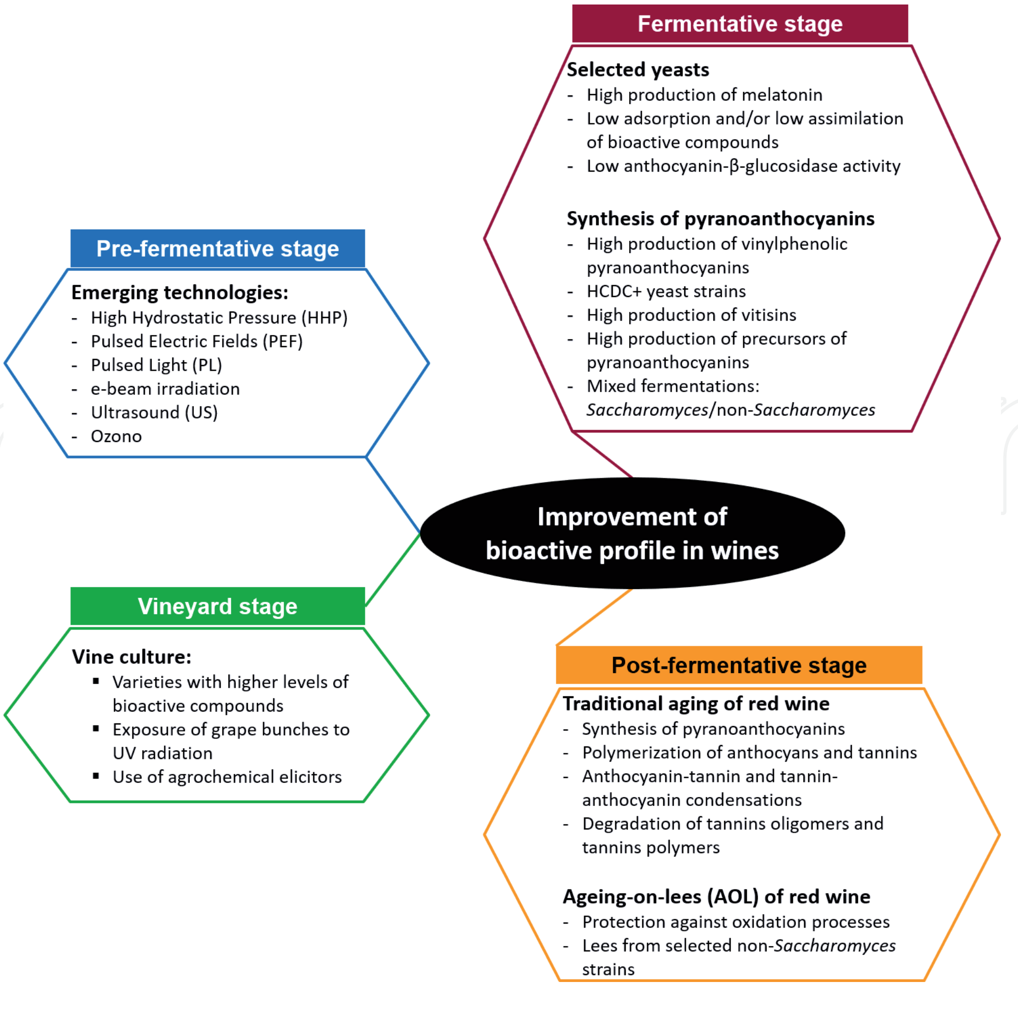

Figure 3.
Technological strategies to improve the content of bioactive compounds in red wines.

Furthermore, the emerging technologies could also be useful. Traditionally, these technologies have been studied to control microbial load of food. However, they can also be useful to improve the extraction of phenolic compounds and other molecules with positive effects on the properties of the wine. Other benefits include aroma preservation and phenolic compound protection against oxidation, since the temperature of the treated product does not change [74] and reduce SO_2 doses, an additive that can cause problems on the consumer's health [75].

These technologies can also help improve the extraction in grapes with low phenolic content, as an alternative to conventional treatments such as the use of pectolytic enzymes or the "blended" with varieties of grapes with higher phenolic content [76]. It also allows to produce wines with greater varietal character, which is preferred in the markets.

3.2.1 High hydrostatic pressure

The high hydrostatic pressure (HHP) technique can improve the extraction and protect the phenolic compounds against oxidation, given that at pressures of 600–700 MPa partial inactivation of the polyphenol oxidase enzyme is achieved [77], which enables the enhancement of the antioxidant properties of wine and, consequently, reduces the SO_2 doses [75]. HHP also allows for the maintenance of the integrity of the berry [74], facilitating the manipulation of the grape, without losses of raw material or risks of microbial contamination.

Pressures of 200 MPa have allowed the enhanced extraction of anthocyanin in red grapes, improving color intensity (26% higher) and total polyphenol index (TPI, 43% higher), with respect to the control [78]. Besides, HHP increases the selective extraction of acylated anthocyanins (up to 68% of *p*-coumarylated anthocyanins), since the HHP reduces the polarity of the grape-must due to the decrease of the water dielectric constant and the pH (molecular deprotonation at high pressures). Thus, the solubility of these anthocyanins is improved.

Higher pressures (600 MPa) were applied by Corrales et al. [79], increasing the acylated anthocyanin extraction by nine times with respect to the control at 70°C. In addition, pulsed electric field (PEF, at 3 kV cm^{-1}) technique was applied, improving the antioxidant capacity by up to three times with HHP and four times with PEF. The latter may be associated with the inactivation of oxidant enzymes.

On the other hand, the HHP favors the formation of pyranoanthocyanins, mainly derived from vitisin A at 600 MPa and 70°C [80]. Nonetheless, the anthocyanin content, like the cyanidin, can be reduced as it occurs with pulsed light (PL) and e-beam irradiation [81, 82].

3.2.2 Pulsed electric fields

The pulsed electric fields (PEF) are efficient in the extraction of phenolic compounds due to its action over the skin cell walls, reaching rates of up to 50% or higher [83], in addition to reducing the maceration time by up to 50% at a dose of 5–10 kV cm^{-1} [84].

Like HHP, the selective extraction of acylated anthocyanins can be increased by more than six times with respect to the control at 3 kV cm^{-1} [79]. Also, a higher degree of polymerization of the skin tannins can be achieved due to the greater permeability and diffusion through the fractured cell walls [85], which reduce the sensation of astringency and bitterness in the produced wines.

Also, the content of flavanols, flavonols, and hydroxycinnamic acids and derivatives can be improved after 12 months of aging in wines obtained from grapes treated with PEF, as obtained by Puértolas et al. [86] when treating Cabernet Sauvignon grapes with doses of 50 a 122 Hz, 5 kV cm^{-1} y, and 3.67 kJ kg^{-1}.

At the level of grape-musts treated with PEF, adverse effects have not been observed at doses of up to 29 kV cm^{-1} [87].

3.2.3 Ultrasound

The ultrasound (US) treatment of red grape-musts is an effective alternative to keep the level of anthocyanins up as high as 97% [88]. This fact clearly shows that the US preserves the chemical stability of these pigments. Combinations of US with heat and ethanol can also be exploited to increase the extraction of total phenols and anthocyanins and to increase the antioxidant capacity [79, 89].

3.2.4 Pulsed light

Pulsed light (PL) is a low-cost technological alternative with higher possibilities of being scaled to an industrial level than HHP, PEF, or e-beam irradiation [81]. Its efficacy varies as a function of the applied light's features. Thus, better performance is achieved with PL than with UV-C, since the former, in addition to its intensity, includes the infrared component [90].

The UV-C light (254 nm, 8.4 kJ m^{-2}, 15 min, 27°C) continuously applied produces micro-cracks in the skin of red grapes [90], inducing a high anthocyanin migration, although it is performed with lesser intensity than with HHP [74] or e-beam irradiation [82] and without affecting the external appearance of the treated berries, which facilitates their subsequent handling.

However, in wines obtained from red grapes treated with PL (12% UV-C, 10% UV-B, and 8% UV-A), a slight reduction of anthocyanins at doses of 10 pulses at 600 J has been noted. This may be associated with the oxidative degradation of these compounds by radiation [82]. Interestingly, vinylphenolic pyranoanthocyanins and vitisins have exhibited higher stability [81].

3.2.5 e-Beam irradiation

Electron beam (e-beam) irradiation can enhance the extraction of anthocyanins by up to 70% at 10 kGy [82], without affecting the external appearance of treated berries. Lower doses (0.5–3.0 kGy) have also shown improvements during extraction of anthocyanins from grape marc [91].

One disadvantage of this technology is the lowering of anthocyanin contents in the produced wines, as consequence of the induced oxidation by radiation [82]. Nonetheless, the content of vinylphenolic pyranoanthocyanins and vitisins is not affected due to the robustness of double bond in heteroaromatic ring under the induced oxidation by e-beam irradiation [82].

3.2.6 Ozone

Grapes exposed to ozone have shown greater contents of flavanols and resveratrol [92, 93]. However, the continuous exposure of berries to this gas (30 μL L^{-1}, 24 h) may produce skin hardening, causing slower extractions without affecting the final content of anthocyanins and flavanols [94].

On the other hand, the efficacy of phenolic extraction has been related with the grape variety. Wines fabricated with grapes containing high level of flavanols (as Nebbiolo) improved their color stability during winemaking procedure, especially with short expositions to ozone (<72 h, 30 μL L^{-1}) [95]. Accordingly, the anthocyanin extraction can be as high as 19% in Petit Verdot grapes treated with ozone, in addition to reduce the fermentation time [96].

3.3 Fermentation level strategies

3.3.1 Selected yeasts

The melatonin content can be increased by using *Saccharomyces* and *non-Saccharomyces* strains with high production of this compound [97], as an additional source to the melatonin coming from grapes [28]. However, some compounds like the phytosterols may be reduced during the winemaking process, since some *Saccharomyces* strains might be able to use them as nutrients [65]. Besides, contents of anthocyanins [98] and resveratrol [99] can diminish, as a result of being adsorbed by the yeast cell walls during the fermentation process.

Another issue to be aware during the winemaking process is the use of yeast with lower expression of anthocyanin-β-glucosidase activity, which is responsible for hydrolysis of anthocyanins [100].

3.3.2 Pyranoanthocyanins synthesis

The most important are vinylphenolic pyranoanthocyanins and vitisins. They present high chemical stability due to the presence of a heteroaromatic fourth ring in their structure, formed by the integration of vinylphenols, pyruvate, or acetaldehyde in the structure of the anthocyanin precursor [101], which provides resistance against oxidation and discoloration in the presence of SO_2 and/or increase of wine pH [102]. Moreover, pyranoanthocyanins possess microbiological stability, for instance, against *Dekkera/Brettanomyces*, since this yeast is not able to hydrolyze these pigments [103].

Fermentations with yeasts with hydroxycinnamate decarboxylase (HCDC+) activity have been studied as a strategy to improve the synthesis of vinylphenolic pyranoanthocyanins, from the condensation of anthocyanins with vinylphenols [101]. The vinylphenols are molecules released from hydroxycinnamic acids in grapes by the HCDC+ activity, which later on can serve as substrate to the synthesis of 4-ethylphenol by *Dekkera/Brettanomyces* [103]. By reducing the content of hydroxycinnamic acids, it is possible to prevent the synthesis of 4-ethylphenol and, in turn, the content of vinylphenolic pyranoanthocyanins can be increased.

Other interesting pyranoanthocyanin groups are the vitisins A and B, which arise from the condensation of pyruvic acid and acetaldehyde, respectively, together with the malvidin during or after the fermentation process [102].

Also, it is possible to increase vitisin A levels with *Schizosaccharomyces pombe* [104], of vinylphenolic pyranoanthocyanins in mixed fermentations of *S. cerevisiae* with *Pichia guilliermondii* [105] or by using species with high production of acetaldehyde, such as *Saccharomycodes ludwigii* [106], to improve the synthesis of vitisin B and other molecules with positive impact on the wine.

On the other hand, it is possible to enlarge the production of acetaldehyde by *S. cerevisiae* in the presence of metabolic inhibitors [71, 107], due to their effect on the alcohol dehydrogenase, which might enhance the synthesis of vitisin B.

3.4 Post-fermentation strategies

3.4.1 Traditional aging of red wine

The aging has direct effects on wine composition, since chemical and/or enzymatic oxidation processes, degradation of phenols on the presence of SO_2, and condensation and polymerization reactions [108], among others, take place at this stage, contributing to modify the content of bioactive compounds.

In general, anthocyanin, resveratrol, and flavonol levels tend to diminish with aging process [1, 108, 109]. So that, more benefits to health are attributed to young red wines. Regarding the resveratrol, hydrolysis of the glycosidic form and cis/trans isomerization take place [108], affecting its availability and activity.

At the same time, the content of pyranoanthocyanins increases through anthocyanin condensation with other molecules [101, 102]. Besides, the anthocyanic polymerization or anthocyanin-tannin condensation can be potentially increased.

Likewise, it can augment the content of monomeric flavanols from the hydrolysis of oligomeric and polymeric forms [1]. In fact, monomeric tannins possess high antioxidant capacity to act against free radicals and chelate metals [4, 5, 8], inhibit oxidative stress in cardiac hypertrophy cases, and inhibit cardiomyocyte apoptosis [110] as well as provide antimicrobial activity against oral pathogens [58].

3.4.2 Aging on lees (AOL)

In the last years, this aging technique has gained relevance in the production of red wine [109]. It consists of the release of polysaccharides from cell walls of selected yeasts lees toward the wine during its stay in barrel [111]. These released polysaccharides can enhance, among other attributes, the protection of phenolic compounds against oxidation, due to the lees that have higher oxygen affinity [112].

Nonetheless, it has been noted that anthocyanin contents can be reduced during AOL [111], especially within the first months of aging. This is a consequence of the adsorbent capacity of lees, particularly, cinnamic anthocyanins [109]. Although the loss of anthocyanins can be reduced with lees of species like *S'codes ludwigii* or *S. pombe* [111].

4. Additional considerations and future perspectives

The protective effect ascribed to bioactive compounds from wine is not only related to only one compound but also to a combined effect of several of these compounds and to their interactions with other compounds present in food. Also, the moderate ingestion of wine is certainly an important factor.

Most studies have been conducted at preclinical levels (*in vitro* and i*n vivo*), aiming to elucidate the action mechanisms. Nonetheless, issues, including the absorption and bioconversion, the number of compounds and their subsequent metabolites in blood circulation, their accumulation and distribution on tissues, the chemical shapes capable of acting on specific receptors in the human organism, and so forth, are still not fully understood.

Despite the existing evidence, there is no consensus regarding its acceptance as an alternative, which aids in the prevention of diseases. Hence, more studies at the clinical level, considering a larger number of volunteers of different ethnicities, lifestyles, and health conditions, are certainly required, with the special consideration that these bioactive compounds cannot be used to replace the medicaments, since they do not possess curative properties, rather they are components of a healthy diet that can help to prevent diseases.

Within the potential strategies, some viticulture practices might contribute to improve the synthesis of bioactive compounds during the vine cultivation. Later into the winery, a proper extraction from the grapes, as well as procedures to minimize the loss of such compounds during the fermentation and aging stages, can improve the bioactive profile of produced wines.

Another important issue is the presence of products such as alcohol-free wines in the markets, which have also shown effectiveness due to the high content of bioactive compounds but with the advantage of avoiding the problems associated with excessive ethanol ingestion.

4.1 Emerging technologies

These kinds of technologies have demonstrated their efficacy to improve the extraction of bioactive compounds in pre-fermentation stages although, until now, some disadvantages have been reported during their application. For instance, the HHP, PL, and e-beam irradiation can diminish the content of anthocyanins like cyanidin in treated grapes [78, 81, 82].

In addition, the high extraction of vitisin derivatives at 70°C by using of HHP, as previously reported by Corrales et al. [80], converts the temperature into a critical parameter that limits its applicability in the winery. This fact indicates the need for more studies to optimize the extraction process.

Likewise, during PL applications [81], it is important to ensure a uniform exposition of the berry surface. The authors suggest the use of roller conveyor belts to change the position of the irradiated berry in order to improve the extraction.

Finally, the scaling of these technologies at the industrial level is still a pending issue since most studies have been carried out in small volumes and in static systems at laboratory level. In order to implement such technologies in wineries, more studies concerning large volumes and continuous flow systems, like the one performed by González-Arenzana et al. [113] with PEF, are needed.

4.2 Pyranoanthocyanins and their effects on health

It has been observed that the antioxidant potential of wine may decrease in aged wines as a result of the reduction of anthocyanins, resveratrol, and flavonols and the simultaneous synthesis of condensation products.

In general, the vitisins have shown lower potential to neutralize free radicals like O_2^- with respect to their anthocyanin precursors [7], while the pyruvic adduct of the delphinidin has shown greater ability to neutralize OH^- and O_2^- when compared with other pyranoanthocyanins.

The pyranoanthocyanin synthesis by incorporation of pyruvic acid in positions 4 and 5 of A-ring in the structure of the anthocyanin precursor can decrease the potential to suppress free radicals, which might be related to the loss of -OH from carbon 5, that together with -OH from carbon 7, favors the antioxidant activity of anthocyanins [114]. These condensations can be achieved at the fermentation level, although these mostly happen during the aging of wine. Thus, in accordance with the traditional winemaking process, these would be necessary as a strategy to provide physicochemical and microbiological stability to the wine.

As in anthocyanin precursor state, pyranoanthocyanins have shown antioxidant and anti-inflammatory activities. For example, against pro-oxidant (H_2O_2) and pro-inflammatory (TNF-α) molecules, in addition to neutralizing the secretion of interleukin 8 (IL-8) in cell cultivation of adenocarcinoma from the human colon [17]. Vitisin A has been shown a protective effect against the secretion of monocyte chemoattractant protein-1 (MCP-1) induced by TNF-α factor in human endothelial cell cultures [115], in addition to show great stability in simulated (*in vitro*) gastrointestinal conditions [116], indicating its potential availability and effectiveness in *in vivo* conditions and at clinical level.

5. Conclusions

There is vast evidence regarding the health benefits of wine, especially red wine, that results from higher contents of bioactive compounds, which aid in the prevention of diseases and provide good health benefits when consumed in moderation. Studies carried out at the pre-clinical and clinical stages have been reviewed, mostly at the pre-clinical level. Therefore, the gathered studies contribute to the better understanding of the action mechanisms by which the bioactive compounds may act in the human organism (clinical level) taking advantage of the antioxidant, anti-inflammatory, antitumor, antithrombotic, and antimicrobial activity, among others, to prevent several diseases.

According to the reviewed literature, studies addressing specific procedures to improve the bioactive profile of wine are still scarce. Hence, we described potential technological strategies that may contribute to the increase in, or at least maintenance of, the levels of different bioactive compounds present in wine during the winemaking process. Starting from the production at the vineyard, cultivation strategies can be applied in order to stimulate the greater synthesis of certain compounds. Once into the winery, the pre-fermentative treatments can increase the extraction of bioactive compounds by treating the grapes with HHP, PEF, LP, US, e-beam irradiation, and ozonization. At the fermentative level, yeasts with low adsorption and/or consumption of bioactive compounds, low anthocyanin-β-glucosidase activity, and high production of pyranoanthocyanins and/or precursor molecules of these, among other strategies, can be utilized. Although, in most cases, the content of bioactive compounds can decrease during the aging period, novel strategies like AOL can help to maintain the levels of these compounds in wines. Also, recurrent chemical processes during aging, despite modifying the structures of the grape compounds, have the advantage of allowing the synthesis of pyranoanthocyanins, polymerization of anthocyanins and flavanols, and anthocyanin-tannin condensations, among others, while maintaining the bioactive profile of the wine to a certain degree. All the above are potential strategies to be considered as technological alternatives that are applicable during the winemaking process, which enhance the content of bioactive compounds in the wine, therefore transferring their benefits to the health of the consumer.

Acknowledgements

This work was funded by the Universidad Privada del Norte (UPN), Project UPN-20191001: Valorización de principios bioactivos y desarrollo de nuevas aplicaciones de excedentes y residuos agroindustriales.

Conflict of interest

The authors declare that they have no conflict of interest.

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