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Review

Derivatization Strategies in Flavor Analysis: An Overview over the Wine and Beer Scenario

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Abstract: Wine and beer are the most appreciated and consumed beverages in the world. This success is mainly due to their characteristic taste, smell, and aroma, which can delight consumer's palates. These olfactory characteristics are produced from specific classes of volatile compounds called "volatile odor-active compounds" linked to different factors such as age and production. Given the vast market of drinking beverages, the characterization of these odor compounds is increasingly important. However, the chemical complexity of these beverages has led the scientific community to develop several analytical techniques for extracting and quantifying these molecules. Even though the recent "green-oriented" trend is directed towards direct preparation-free procedures, for some class of analytes a conventional step like derivatization is unavoidable. This review is a snapshot of the most used derivatization strategies developed in the last 15 years for VOAs' determination in wine and beer, the most consumed fermented beverages worldwide and among the most complex ones. A comprehensive overview is provided for every method, whereas pros and cons are critically analyzed and discussed. Emphasis was given to miniaturized methods which are more consistent with the principles of "green analytical chemistry".

Keywords: derivatization; sample preparation; volatile odor-active compounds; odor; aroma; flavor; wine; beer; green analytical chemistry

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1. Introduction

Regarding the definition of "odor" or "smell", most scientific publications define it as the response of the olfactory system in which a volatile compound reaches the epithelium determining a stimulus thorough the nasal way [1,2]. Similarly, volatile molecules can interact with the odor receptors also flowing from the mouth along the retro-nasal way: this second case, which takes place during consumption and gives a relevant contribution to "taste" is the definition of "aroma" [3]. Smell and aroma, whose sum including taste is called "flavor", are responsible for almost two of the most important senses for consumers' appreciation of food and beverages: Therefore, in addition to safety purposes, the measurement of flavor compounds is mandatory for industry and producers. This is particularly crucial for beverages, where most of the attention is focused on flavor [4,5].

Flavor is an identity aspect for beverages since it allows the consumer to differentiate products based on the origin of raw materials (e.g., different grape varieties for wines, different plant cultivars of coffee), production proceedings (e.g., different beer styles or different coffee extractions), or age (e.g., ageing of wines) [6]. To determine the dimensions of the drinking products industry, the worldwide average production of wine in the last 20 years estimated by the International Organization of Vine and Wine (OIV) was 269 Mhl [7] with a turnover of USD 381.3 billion [8]. On the other hand, the Brewer Association in its annual release reported a worldwide production of 284 billion liters of beer, accounting for USD 100.2 billion of market value [9]. This trend, which can be

easily extended to other drinking products, highlights the economical, industrial and social magnitudes of beverage business and underlines the importance of related activities such as analytical chemistry for quality control and R&D purposes. Consistent with what was reported above, the determination of volatile odor-active molecules (VOAs) in drinking products has become one of the key application fields for analytical chemistry [10].

Beverages, which are mainly homogeneous liquid mixtures (or close to homogeneous), differentiate each other because of the broad variability of analytes' concentration and matrix composition; these differences, in addition to other minor aspects, make VOAs' analysis still a demanding task. Even though the nuances detected by the human nose could be summarized by well-defined flavors associated with other edible products, from the chemical point of view the number of odor and aroma substances in beverages is huge. In addition, odor intensity is related to both concentration and olfactory threshold, which means that a flavor substance could provide a strong odor intensity independent of its concentration. This is a prevalent situation for beverages where VOAs' concentration ranges from a few ng·L^{-1} to hundreds of mg·L^{-1} and are enclosed in complex and diversified matrices where potentially interfering components can modulate their olfactory effectiveness [11–13].

Based on the issues listed above, it is clear that analyzing odor-active compounds is as important as it is tricky. A great effort was dedicated by the scientific community to develop and improve analytical procedures to make flavor analysis in compliance with the needs of the productive world: in the early years, when food analysis grew in its importance, the main task was to improve reliability and performance. In more recent times, after the analytical methods for most flavor compounds became satisfactory, the attention was shifted to make procedures fast, inexpensive, efficient, and green.

Why Do We Still Have to Do Derivatization?

For both odor and aroma, only compounds capable of reaching the epithelium and interacting with it are defined as "active". These molecules must be volatile for moving to the receptors and have a suitable structural shape for fitting the detection sites. Leaving out the last aspect, which concerns only molecules already in the gas phase, the volatility restriction limits the set of possible VOAs to smaller ones with reduced polarity and low molecular weight [14]. Because of these characteristics, the most suitable techniques for VOAs' analysis are based on gas chromatography (GC) [15,16]. GC can be coupled to various detectors, spanning from non-specific ones like the flame ionization detector (FID) and electron capture detector (ECD) to more complex and specific ones like mass spectrometry (MS), especially for untargeted purposes [17]. Analytes suitable for GC analysis are volatile and semi-volatile molecules, which is also one of the main characteristics of VOAs, making this technique the first choice in aroma determination. Electron ionization (EI) source makes MS a powerful tool in compound discovery and a reliable detector to balance matrix effects [18]. Unfortunately, in addition to flavor compounds, beverage composition comprises macromolecules, proteins, polysaccharides, lipids, metal ions, non-volatile compounds, and often solid particulates which are inappropriate substances for GC injections and must be removed before analysis [19]. In addition, since beverages are mainly composed of water, which is unsuitable for GC analysis, all analytes must be collected into a suitable injection carrier. These requirements make preliminary steps like liquid–liquid extractions (LLE) or solid-phase extractions (SPE), mandatory to remove interference and to concentrate analytes in non-polar organic solvents suitable for GC injection [20–22]. In contrast, implementing further preliminary operations contributes to measurement errors and adds costs, consumption of time, production of waste, as well as an overall increase in complexity.

Recently, a huge breakthrough in this field was provided by the development of solventless methods such as solid-phase micro-extraction (SPME) and stir bar sorptive extraction (SBSE) [23,24]. These techniques are based on the adsorption of analytes onto a coated surface (fiber for SPME, stir bar for SBSE) which preconcentrates and extracts them

from the sample, avoiding the use of solvents and minimizing the production of waste [25]. SPME can be both immersed into the sample (for less volatile analytes [26]) or exposed to its vapors to give a consistent representation of the aroma composition [27]. However, the aforementioned advantages of solventless techniques are limited by some factors: first, the diverse affinity of various coatings against different classes of analyte makes the adsorption efficiency class-dependent, with an evident lack in terms of representativity [28]. Furthermore, due to the different concentration of molecules in samples, coatings are often saturated by the most abundant compounds, which results in a decrease in efficiency for trace analytes [29].

In the last two decades, the development of atmospheric pressure ionization sources (API) for mass spectrometry, such as atmospheric pressure chemical ionization (APCI) and (especially) electrospray ionization (ESI) extended aroma determination to the liquid side of analytical chemistry. Liquid chromatography (LC) coupled to mass spectrometry (MS) is suitable for the analysis of less volatile odorants which give poor response with GC methods, and sometimes this allows a simplified sample preparation prior the analysis, since aqueous samples can be directly injected in reverse phase chromatography after a simplified preparation. In this case, the range of suitable analytes is strongly limited by the ionization mechanism on which the API sources are based: ions are formed as products of the acid-base reaction or adduct formation [30]. Only polar and properly functionalized molecules can be involved in this kind of reaction, whereas many VOAs are non-polar hydrocarbons (e.g., terpenes and some norisoprenoids) or low polar small molecules with no more than one polar functional group (e.g., terpenoids, volatile carbonyls, thiols, esters, alcohols, carboxylic acids) [31–33]. Novel LC-EI-MS interfaces like Direct-EI, Liquid-EI, supersonic molecular beam (SMB), or Cold-EI could be a good alternative for balancing drawbacks of conventional techniques but, to date, have not yet been used in VOAs' analysis [34–38].

Summarizing, excluding non-conventional bench scale approaches, GC- and LC-based instruments are the most widely used devices for VOAs' analysis, both with different strengths and applicability restrictions but with a strong complementarity. So, why is the use of derivatization still a key point for some methods? Here the most important reasons are reported:

1. Derivatized analytes have an increased instrumental response factor. Thiols analysis with LC-MS is emblematic; the sulphur group allows these molecules to be easily ionized using ESI sources, but, due to their ultra-low concentration in beverages, derivatization boosts the analytical response, improving the limits of detection and quantitation down to $ng \cdot L^{-1}$ [39].
2. Derivatized analytes have an increased extraction efficiency. Some molecules are quite hydrophilic, so their flavor is mostly due to their olfactory response rather than abundancy in the vapors. It means that after derivatization, it is possible to achieve a less polar compound with higher volatility and a stronger affinity to extraction solvents, cartridges, or fibers [40].
3. Derivatization can modify chemical and structural molecular characteristics to improve extraction selectivity [41]. A reduction in complexity, matrix effects, and purification steps needed is achieved.
4. Derivatized analytes have a different reactivity, so derivatization can be intended also as a preservative process for unstable compounds [42]. This argument can be extended also to strongly volatile compounds, which can be stuck and stabilized in derivatized form into the samples.

The contemporary trend in analytical chemistry is directed towards the removal of as many steps as possible, and derivatization, together with all sample preparation procedures, is included in the pool of operations to be avoided as much as possible [43]. However, as previously mentioned, many of the best-performing analytical protocols for VOAs' determination in beverages still involve derivatization, the use of which could also be intended as a good alternative to improve the overall efficiency.

This review aims to be a snapshot of the most commonly used derivatization strategies for VOAs' determination in wine and beer, the most consumed fermented beverages all over the world but also among the most complex ones. A comprehensive overview is provided for every method, whereas pros and cons are critically analyzed and discussed.

2. Derivatization of VOAs in Wine and Beer Analysis

Most VOAs in wine and beer can be extracted and analyzed as they are, so derivatization concerns only a restricted pool of molecules. It must be highlighted that the need for derivatization is not only class-dependent but also structure-dependent. There are analytes belonging to the same group that could require or not require derivatization, depending on the olfactory threshold and volatility. To date, the most frequently derivatized VOAs are thiols, carboxylic acids, carbonyls, and some other extra compounds with particular characteristics. Early derivatization procedures involved transition metals or hazardous substances with consequent environmental and safety issues. The current approaches discussed below are based on organic or organometallic agents (Figure 1) with increased selectivity, yields, and reduced drawbacks.

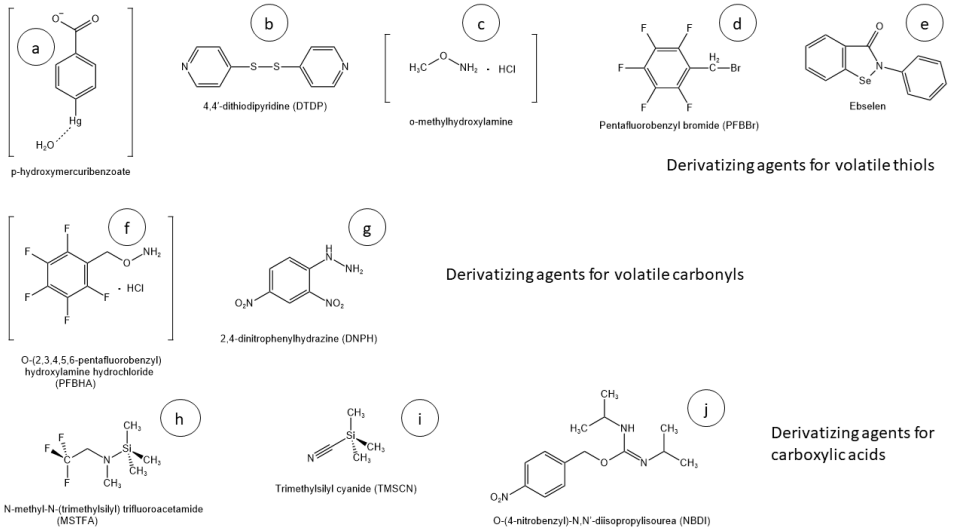

Figure 1. (**a**–**j**) Chemical structures of most relevant derivatizing agents currently in use in VOAs' analysis.

2.1. Volatile Thiols

Volatile Thiols (VTs), also known as mercaptans, are odor-active molecules functionalized with a R-SH functional group belonging to the broad category of Volatile Sulphur Compounds (VSCs). These compounds give a significant contribution to beverage aroma thanks to their broad presence and low Odor Detection Threshold (ODT) [44]. Despite their important contribution, VTs are present in parts per trillion ($ng \cdot L^{-1}$) levels, so an enrichment technique and a sensitive instrument are mandatory to perform analysis [44–46]. In addition, due to the Sulphur reactivity, their concentration can be affected by several reactions and equilibria that take place in the matrix [40,47], which makes derivatization unavoidable. It must be underscored that extraction parameters which are labelled as huge for other green techniques must be reconsidered for VTs due to their peculiar characteristics.

Derivatizing methods had different focuses depending on the instrumental technique used. If the quantification was performed with GC, the aim was to increase volatility, whereas if it was performed with LC, the task was to increase the response of the detector. In all procedures the derivatizing agent reacted with the -SH group that, in free form, made the analyte highly reactive and unstable.

Historically, thiols were known to show a strong affinity for mercury (Hg+) and silver (Ag+), so first procedures were developed using these metal ions as highly selective derivatizing agents. Curiously, the word mercaptan itself derive from the Latin forms cercurium captans, which means mercury-seizing [46]. Shifting to more recent times, tra-

ditional GC-based methods involve the use of metal ions or hazardous organomercurial agents like p-HMB (p-hydroxymercuribenzoate), require pH adjustment, large extraction volumes (over hundred mL), and are highly time-consuming (Figure 1a) [48]. Five hundred mL of wine are adjusted to pH 7 with sodium hydroxide and extracted 2 times with 100 mL of dichloromethane; the organic phase is then extracted with 20 mL of p-hydroxymercuribenzoate aqueous solution, keeping pH > 7. The resulting solution is finally purified and concentrated in a preparative column, eluted in dichloromethane again, and injected in GC-MS. The most relevant aspects of this and the following methods are reported in Table 1. This procedure is highly time-consuming and requires huge volumes of sample and hazardous solvent, with consequent production of more than 1 L of waste per sample [49]. However, this was the method which allowed the first instrumental studies on VTs' occurrence in wine and, for over 10 years from its presentation, did not have any alternative [50–52].

HS-SPME methods coupled to GC-MS-based techniques were interesting due to the high automation, avoided use of solvents, and the requirement of less than 20 mL of sample. Pentafluorobenzyl bromide (PFBBr) was successfully used as a derivatizing agent because, despite its toxicity, its selectivity and reaction efficiency require just a low amount of reagent, minimizing possible safety drawbacks (Figure 1d) [53]. PFBBr has a bromide atom bound to a benzylic primary carbon that perfectly matches with the requirements of nucleophilic substitution; in this case, the thiolic -SH acts as the nucleophile and replaces the Br leaving group, giving a more volatile and less polar product that better fits for gas chromatography (Figure 2a) [54].

Thanks to its promising results, the same derivatizing agent was also used in a miniaturized LLE protocol [55] and a miniaturized SPE one [54]. HS-SPME was also used with direct in situ derivatization using o-methylhydroxylamine hydrochloride and stable isotope dilution assay [56], obtaining an impressive LOD of 0.19 ng·L^{-1} for 4-MSP in white wine. In this case, only 4-MSP was evaluated, because the o-methylhydroxylamine reacted with the carbonyl group instead of the -SH group (Figure 1c).

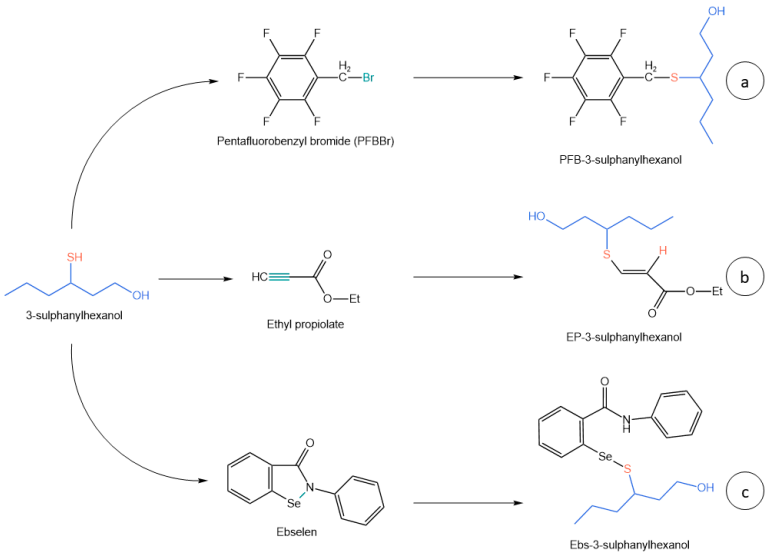

Figure 2. Different derivatization pathways in VTs' derivatization. (**a**) Reaction with PFBBr; (**b**) Reaction with ethyl propiolate; (**c**) Reaction with ebselen.

Ethyl propiolate (ETP) was another interesting derivatizing agent used for thiol GC analysis. His reactant was a greener alternative to the most used PFBBr based on a different chemical mechanism. In this case, the thiolic analyte was added in alkaline pH (>10) to the triple C-C bond of ETP with an anti-Markonikov regioselectivity (Figure 2b). Stir bar sorptive extraction (SBSE), which was an emerging green technique, was used coupled to in situ ETP derivatization and thermal desorption GC-MS/MS; that was one of the greenest methods developed up to now for thiols that covers a broad range of analytes with

proper sensitivity [57]. However, in the last decade, the focus has moved to preparation techniques suitable for coupling with LC-MS, which granted boosted sensitivity, simplifying the analyte isolation. Derivatization with 4,4′-dithiodipyridine (DTDP) takes place at mild acid conditions providing stable non-volatile molecules which are suitable for SPE isolation with a C18 extracting phase [58]. DTDP reacted directly with -SH, producing an organosulfur molecule with a pyridinic site used to enhance ionization efficiency for ESI (Figure 1b). With a similar procedure, it is also possible to isolate enantiomers in a different type of wine, which are known to provide different nuances, just by using an Amylose-1 chiral column [59]. The SPE method described above was the progenitor of many other procedures: in the "greenest" one, the conventional LC was replaced by convergence chromatography (CC), which is a type of supercritical fluid chromatography (SFC) where CO_2 and methanol are used as a mobile phase [60].

Table 1. GC-MS and LC-MS methods presented for VTs' determination and related highlights.

Article	Year	Matrix	Ext. Volume	Ext. Technique	Der. Agent	Instrumentation	Pro & Cons
[48]	2003	White wine	500 mL	LLE + N_2 concentration + preparative column	p-HMB	GC-EI-MS	+ 5000 concentration factors − 100 mL of hazardous solvent
[53]	2006	White wine	20 mL	HS-SPME with on-fiber derivatization	PFBBr	GC-NCI-MS	+ Solvent-free − Time-consuming derivatizing process
[55]	2007	White wine	6 mL	LLE with benzene	PFBBr	GC-NCI-MS	+ No equipment required − Time-consuming, hazardous solvent
[54]	2008	White wine	20 mL	SPE and SIDA	PFBBr	GC-NCI-MS	+ Good performance − Disposable cartridge, use of solvents
[56]	2014	White wine	3 mL	HS-SPME with in-situ derivatization	o-methyl-hydroxylamine hydrochloride	GC-EI-MS/MS	+ Low LOD, high automation, low sample volume − Only 4-MSP
[57]	2015	Beer, hops, wort	10 mL	SBSE-PDMS with in-situ derivatization	Ethyl propiolate	GC-EI-MS/MS + GC-EI-QTof	+ Low LODs, many analytes, solvent-free, safe reagents − Instrumentation complexity
[58]	2015	White wine	20 mL	SPE with Bond-Elut C18, and SIDA	DTDP	LC-MS/MS	+ Relevant VTs, accuracy − Disposable cartridge
[59]	2018	Wine (all)	20 mL	SPE with Bond-Elut C18, and SIDA	DTDP	LC-HRMS	+ Enantiomer analysis − Disposable cartridge
[60]	2018	Red wine	20 mL	SPE with Supelclean ENVI-18	DTDP	GC-MS/MS	+ Greener chromatography − Disposable cartridge, complexity
[61]	2015	Wine, beer	20 mL	LLE with 4 mL of CH_2Cl_2	Ebselen	LC-HRMS	+ No equipment required, flexibility, performance − CH_2Cl_2, time-consuming
[62]	2018	White wine	35 mL	LLE with ethanol	Ebselen	LC-HRMS	+ No equipment required, safe solvent − high sample volume, filtration
[63]	2017	White wine	100 mL	SPE, 20 mg Li-Chrolut EN	Ebselen	LC-HRMS	+ Minimized cartridge, accuracy − High sample volume
[39]	2022	White wine	35 mL	Micro LLE + 0.22 µm filtration	Ebselen	LC-MS/MS	+ Performance, reduced volumes − Low automatability

Even though DTDP and other derivatizing agents have been successfully used for VTs' analysis, 2-phenyl-1,2-benzisoselenazol-3-one (ebselen) is the one which showed the best selectivity, efficiency, versatility, and stability. Ebselen reacts with thiols in acidic medium, simultaneously protecting the -SH function from oxidation and increasing the affinity of the derivatized molecule for the extraction solvent by the formation of a positive charge in the nitrogen atom of the derivatizing agent (Figure 1e). The reaction mechanism (Figure 2c) is based on the Se-N bond cleavage of ebselen by the thiolic function and the following

formation of the corresponding selenenyl sulfide Se S bond [64]. The exchangeable hydrogen of the amidic function contributes to the enhanced ionization efficiency in ESI sources, resulting in an improvement of the method response [65].

Vichi et al. first published a method for olive oil [66] that was subsequently also tailored for brewed coffee [67], beer, and wine [61]. These protocols did not involve disposable consumables but require the use of small amounts of dichloromethane, which is not a green solvent. A similar procedure was presented for wines replacing dichloromethane with ethanol, but with a higher volume of sample (35 mL instead of 20 mL) [62]; this method was further optimized, achieving LODs and LOQs suitable for the analysis of VTs also in non-varietal wines [39].

2.2. Volatile Carbonyls

Volatile carbonyl compounds (VCCs) are fundamental components in the flavor of all fermented beverages. Because of their low odor perception threshold, these molecules are responsible for a strong olfactory impact even at low concentrations [68,69]. VCCs, both aldehydes and ketones, originate as products of Maillard reactions, Strecker degradation, aldol condensation, and lipid oxidation [70] but also from biological processes like alcoholic fermentation. Because of that, these molecules are among the most relevant VOAs in fermented beverages [33,71]. A content of VCCs slightly above the olfactory threshold is related to aromatic and pleasant nuances of vanilla, caramel, butter, honey, potato, orange, lemon, violets, cider, and plum [19,72–79]. Conversely, higher concentrations are associated with oxidation, which is a long-standing undesired problem responsible for aroma defects [80–82].

From the analytical point of view, VCCs' quantification is affected by two main issues. First, thanks to the presence of a functional group suitable for receiving the hydrogen bond, these molecules are among the most hydrophilic VOAs [82]. In addition, the average concentration in principally fermented beverages is comprised between hundreds of $ng \cdot L^{-1}$ and a few $\mu g \cdot L^{-1}$, so the amount in the vapors is significantly low [19].

Most current methods were based on heterogeneous extraction (SPE or SPME) and GC-MS quantification [20]. For what concerns SPE, Mayr et al. developed a GC-MS/MS quantitation method for 18 carbonyl compounds based on O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine hydrochloride (PFBHA) derivatization on cartridge [83]. PFBHA is an efficient and selective agent that reacts with carbonyl function through a nucleophile addiction, giving an oxime-like product (Figure 1f) [41]. Even though this method showed high performance in terms of sensitivity and linearity, the SPE procedure was expensive, time-consuming, and scarcely automatable, in contrast to the rules of green analytical chemistry [84]. To overcome these limits, many other methods were based on the Head Space Solid Phase Micro Extraction technique (HS-SPME). This straightforward strategy does not involve any preliminary manual operation and combines high productivity and satisfactory performance [85]. HS-SPME methods were purposed with PFBHA on-fiber derivatization [86] and in-solution derivatization [87,88], both with satisfactory results but different simplicity of execution. Similar methods were also used to perform carbonyl quantitation in beers [68].

On-fiber derivatization (OFD) was applied for the determination of staling 15 aldehydes in wort and beer samples using PFBHA and GC-EI-MS/MS [89]. This procedure demonstrated an improved sensitivity over a broad calibration range (0.01–1000 $\mu g \cdot L^{-1}$) and reduced matrix effects resulting from overlapping PFBHA-oximes (PFBOs). Extensive validation through linearity assessment ($R^2 > 0.99$), LOD/LOQ, precision (RSD < 9.2%), and recovery (80–118%) was provided to support the protocol. The procedure is very simple; 3 mL of decarbonized beer, 1 g NaCl, and 10 min at 50 °C of fiber exposure previously soaked with the derivatizing agent. A preliminary version of this method was presented some years before by Schmarr et al. for the determination of many VCCs in wine; in this case, a wider range of analytes was analyzed comprising alkanals, €-2-alkenals, (E,E)-2,4-

alkadienals, and others, including S-containing ketones [87]. This procedure required 10 mL of untreated sample and 20 min of following head-space extraction at 40 °C.

In recent times, on-solution derivatization (OSD) grew in importance and became the strategy of choice for newly developed methods. Regarding wines, it was implemented into a new analytical method for the determination of 18 VCCs using HS/SPME and GC-IT-MS [85]. After evaluating five fiber coatings, extraction parameters, and matrix characteristics (pH, ionic strength, tannins, anthocyans, sucrose, SO_2, and alcoholic degree), the authors found the best performance using 2 mL of sample (previously saturated with NaCl), 50/30 µm DVB/CAR/PDMS fiber, and 45 min at 40 °C. Good linearity ($R^2 > 0.998$), remarkable repeatability and reproducibility (RSD < 5.5%), and LOD ranging from 0.62 µg·L^{-1} to 129.2 µg·L^{-1} were achieved. Moreira et al. used OSD with the PFBHA and HS-SPME method coupled to GC-MS/MS for the quantification of 38 VCCs in different categories of Port wines [87]. Port is a Portuguese beverage considered to be one of the most representative products within oxidized wines. This product is known to be rich in carbonyls and sugars, so many issues like matrix effect, carryover, and fiber saturation must be considered. Optimal extraction conditions were by using 2 mL of wine extracted using a 65 µm PDMS/DVB fiber under stirring for 20 min at 32 °C. The method was also supported by robust validation. Moreira et al. also presented a similar procedure based on PFBHA as the derivatizing agent for the determination of 45 different VCCs in beer [68]. This protocol was a fully automated HS-ISD-SPME. The fiber was a 65 µm PDMS/DVB, which was used to extract 5 mL of beer at 45 °C for 20 min without salt addition. This method showed to be linear, precise, accurate, and sensitive. LODs ranged from 0.003 to 0.510 µg·L^{-1}, except for furans, which showed higher values (1.54–3.44 µg·L^{-1}), whereas LOQs varied from 0.010 to 1.55 µg·L^{-1}, except for furans (4.68–10.4 µg·L^{-1}). Good repeatability was achieved (RSD < 17%) for all analytes. Accuracy was measured evaluating recovery in spiked samples which ranged from 88% to 114%. Relevant aspects of the methods discussed above are reported in Table 2.

Table 2. GC-MS and LC-MS methods presented for volatile carbonyl determination and related highlights.

Article	Year	Matrix	Ext. Volume	Ext. Technique	Der. Agent	Instrumentation	Pro & Cons
[86]	2008	Wine	10 mL	HS-OFD-SPME – 65 µm PDMS/DVB	PFBHA	GC-IT-MS	+ Broad range of carbonyls, no salt addition – Large sample volume, no real application presented
[85]	2010	Wine	2 mL	HS-ISD-SPME – 50/30 µm DVB/CAR/PDMS	PFBHA	GC-IT-MS	+ Performance, robust validation, automatable – Limited range of carbonyls
[87]	2019	Wine	2 mL	HS-ISD-SPME – 65 µm PDMS/DVB	PFBHA	GC-MS/MS	+ Wide range of VCCs, robust validation, efficient, reliable – No diketone was quantified, used in analyte-rich matrix
[68]	2013	Beer	2 mL	HS-ISD-SPME – 65 µm PDMS/DVB	PFBHA	GC-IT-MS	+ Strong validation, efficient, reliable – Proof of application with a reduced number of samples
[89]	2019	Beer	1 mL	HS-SPME – 50/30 µm DVB/CAR/PDMS	PFBHA	GC-MS	+ Wide range of polar analytes – Long extraction time, reduced productivity
[90]	2022	Beer	-	-	DNPH	LC-HRMS	+ No sample prep, huge innovation – Performance under HS-SPME with PFBHA

Like for many other VOAs except volatile thiols, liquid-chromatography was not the gold standard for quantitative approaches for volatile and low polarity. Recently, Peng et al. released an unconventional LC-HRMS method based on 2,4-dinitrophenylhydrazine (DNPH) derivatization for the quantification of methanal, ethanal, propanal, and n-butanal in beer (Figure 1g) [90]. The derivatizing agent reacts with the carbonyl function through an

addition–elimination mechanism producing an imine product [91,92]. Despite the overall performances for the four aldehydes considered in this study ($R^2 > 0.95$, LODs at ng·L^{-1} level, RSDs $\leq$ 8.4%), the main goal was related to the derivatization reactions which took place between drops generated by two microdroplet sprays. This method provided a huge innovation over conventional approaches but still appeared in preliminary state (only four analytes considered), so it must be further improved to be extended to daily practice.

2.3. Carboxylic Acids

Carboxylic acids (or fatty acids) are hydrocarbons functionalized with a carboxyl group whose presence in fermented beverages originates from raw materials (mostly from the firm tissues of fruits) and, especially, during alcoholic fermentation [93]. Due to the strong hydrophilic interactions established by the carboxyl group with the matrix, most of them are non-volatile and odorless [94]. Despite that, some short-chain carboxylic acids are volatile enough to move into the vapors and to cause olfactory activity. As it happens for many VOAs, carboxylic acids are identified with desired flavors for some products like sour beers [95], whereas with a higher concentration, they are related to unpleasant acrid and repulsive nuances [96].

Conventional fatty acid quantitation was performed with an extraction followed by derivatization to methyl esters and GC-MS analysis [97]; in this case, the extraction was performed using methanol, which also had the function of a derivatizing agent for thorough esterification in acid conditions [98,99]. This method, which was developed over 30 years ago and is still in use, was affected by the simultaneous transesterification between methanol and ethyl esters present in the samples; this issue determined an increased amount of free fatty acids and a non-representative measurement of other VOAs. Gallart et al. presented an alternative procedure based on methylation for a precise quantitation of free fatty acids, spanning from C6 to C18 [100]; these are key compounds for wines and beers, since C6 (caproic acid), C8 (caprylic acid), and C10 (capric acid) are important VOAs because of their flavors of rancid cheese and goat-like flavors, which are unpleasant already at a high concentration. In this upgraded protocol, the extraction was performed in triplicate using hexane (5 mL), the sum of aliquots was then centrifuged and concentrated to 1 mL under a nitrogen stream, and finally 1 mL of derivatizing solution (sulfuric acid (3%) in methanol) was injected and allowed to react for 3 h at room temperature. This procedure was more complex but made the quantitation of free fatty acids feasible and precise.

In more recent times, silylation of the carboxyl function was implemented as a selective derivatization strategy for the analysis of free carboxylic acids. This procedure was used in many other matrices before and only in the last ten years was extended to beverages [101]. Silylation proceeds via bimolecular nucleophilic substitution (SN2) on the silicon atom (electrophile) where the carboxyl group acts as the nucleophile that replaces a part of the derivatizing reagent (leaving group). The aim of this process is to hide the hydrophilic carboxyl function and to simultaneously lower the polarity and increase the volatility [102]. Browsing published literature within all developed reactants for silylation purposes, only two of them were used in beverages. Gullberg et al. optimized a method based on the use of [N-methyl-N-(trimethylsilyl) trifluoroacetamide] MSTFA, the application field of which was the metabolomics of plant leaves (Figure 1h) [103]. The authors implemented a lyophilization (10 h at room temperature) prior to sample drying, dissolution in methoxyamine hydrochloride (20 mg·L^{-1} in pyridine), silylation with MSTFA for 30 min at 37 °C, and a final filtration. This method demonstrated a significant efficiency and good versatility (amines and monosaccharides were also simultaneously derivatized).

Differently, Khalimov et al. explored the use of trimethylsilyl cyanide (TMSCN) instead of MSTFA (Figure 1i). In a metabolomic study on blueberry fruits published in 2013, they tested TMSCN and MSTFA, both with and without preliminary methoximation treatment, and demonstrated up to 8.8 times higher peak intensities with TMSCN compared to MSTFA [104]. Because of that, the same research group extended the TMSCN-based

procedure to wine, achieving exciting results; 5 µL of wine was first dried under a vacuum for 2 h at 40 °C, spiked with a 10 µL solution of methoxyamine hydrochloride (40 mg·L^{-1} in pyridine), and agitated at 40 °C for 90 min at 750 rpm, then spiked with 40 µL TMSCN and agitated at 40 °C for 40 min at 750 rpm. Thanks to the obtained efficiency, it was possible to achieve satisfactory performance even producing just of 55 µL of waste (Figure 3) [105]. Interestingly, all these procedures are derived from others developed mainly from metabolomic studies on plants. In addition, no fatty acid determination for other fermented beverages like beer was found in literature performed with derivatization, probably because the different average concentration and matrix composition make conventional HS-SPME-GC-MS satisfactory without supplementary steps [96,106–108].

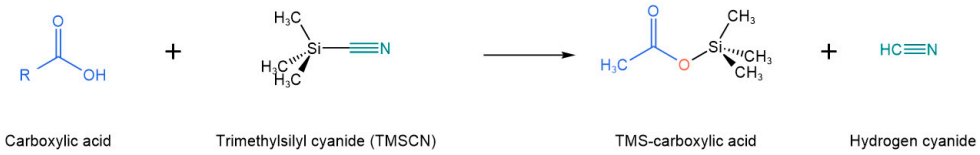

Figure 3. Example of silylation reaction used in the derivatization of odor-active carboxylic acids.

The methods discussed above were all based on gas-chromatography, because in LC-MS determination, carboxylic acids perfectly match the ionizability requirements of API sources. Because of that, only one procedure for liquid chromatography involving derivatization in the explored literature was based on UV determination. Cunha et al. (2002) used O-(4-nitrobenzyl)-N,N′-diisopropylisourea (NBDI) for the determination of carboxylic acids in must and Port wine, which are tricky matrices because of their significant sugar content (Figure 1j) [109]. The procedure is very simple; 5 mL of the sample were preliminarily treated for 15 min with 0.5 g of activated strong cation exchange resin (Dowex 50W-X8) to remove interferences, then 50 µL of the resulting solution was spiked with 500 µL of a solution of NBDI in dioxane (10 g·L^{-1}) and heated at 80 °C for 60 min. The resulting solution was diluted with 2 mL of acetonitrile, treated again with cationic resins to remove the exceeding reactant, and filtered through 0.22 µm prior to the injection. In this case the reaction did not increase the analyte volatility in the way that GC-based procedures did but links a strong chromophore to make linear molecules UV-detectable [110,111]. This procedure is very interesting because it is still a good alternative to MS-based protocols, does not require expensive instrumentation, and gives good performance with viscous matrices. This last method along with all previously mentioned methods are listed in Table 3.

Table 3. GC-MS and LC-MS methods presented for carboxylic acid determination and related highlights.

Article	Year	Matrix	Ext. Volume	Ext. Technique	Der. Agent	Instrumentation	Pro & Cons
[98]	1989	Spark. wine	1 mL	6 mL MeOH + 2.5% v/v H_2SO_4	MeOH + acid catalysis—70 °C, 90 min	GC-FID	+ Easy, no expensive agent required − Unsuitable for free fatty acids fraction
[100]	1997	Wine, must	50 mL	3 × 5 mL hexane + concentration under N_2 stream	1 mL MeOH + 3% v/v H_2SO_4 Room T°, 180 min	GC-FID	+ Allows determination of free fraction − Many steps, complex, time-consuming
[111]	2018	Red wine	100 µL	Lyophilization + drying/dissolution	70 µL MSTFA—37 °C, 30 min	GC-EI-MS	+ Miniaturized volumes, suitable for other compounds − Lyophilization needed, many steps
[105]	2022	White wine	5 µL	Drying/dissolution, methoxymation	40 µL TMSCN—40 °C, 40 min	GC-EI-MS	+ Miniaturized, negligible waste, efficient − Time-consuming, many steps
[109]	2002	Fortified wine, must	5 mL	Double cationic resins clean-up	500 µL NBDI (10 g·L^{-1})—80 °C, 60 min	HPLC-UV	+ Based on HPLC-UV, robust, cheap − Time-consuming, many steps

2.4. Other VOAs

Among all VOAs in wines and beers, there are some which are nowadays usually analyzed with procedures that do not involve derivatization; however, derivatization-based procedures were also developed in the past for compensating for reduced instrumental sensitivity or matrix effects. These strategies can be interesting today for further improving performance in highly difficult tasks or complex matrices.

Volatile phenols (VPs) are VOAs with reduced olfactory thresholds known to provide a relevant contribution to many important foods and beverages [112]. These molecules naturally derive from the aromatic amino acid phenylalanine, but their formation could be also induced by heating treatments before fermentation [113]. Within this class of compounds, there are some molecules (guaiacol and 4-methylguaiacol in particular, but also cresol, syringol, and methylsyringol) that are the molecular fingerprint of the aroma defect "smoke taint"; on the other hand, volatile phenols are extracted from wood and so are ubiquitous molecules in beverages submitted to barrel refining [114,115]. Because of the physical (low boiling point) and chemical properties (acid phenolic function), these compounds are directly suitable for GC-MS and LC-MS determination [11,116]. However, there are some literature applications where VPs were submitted to derivatization. Soleas et al. presented a method based on the silylation of phenols to be applied on wine and beverages using BSTFA (bis(trimethylsilyl)trifluoroacetamide) as a derivatizing agent [117]. Based on this article, Minuti et al. developed a simple procedure using 100 mL of wine acidified to pH 2 extracted with 100 mL of ethyl acetate; the extract was dried, evaporated to 1 mL under a gentle nitrogen stream, and spiked with 50 µL of BSTFA (bis(trimethylsilyl)trifluoroacetamide) for the derivatization [118]. As many as 22 phenols, including also some VPs, were quantified using GC-MS over a broad calibration range. However, the methods presented above required many steps, some of them very laborious and tricky [119].

One of the most interesting is the method presented by Allen et al. for the quantitation of 22 VPs in grapes and wine using SPE prior to derivatization with trimethylchlorosilane (1% v/v bis-silyltrifluoroacetamide) to perform a silylation of the -OH function (BSTFA/1% TMCS). The authors demonstrated high analytical performance just using a single quadrupole GC-MS with SIM acquisition thanks to the improved detectability of sylanized analytes [120]. The procedure was completely conducted by the autosampler, so precision and productivity were maximized. However, because of the widespread availability of tandem mass spectrometry in most analytical facilities, and in compliance with sustainability requirements, derivatization-based procedures have been almost totally replaced by direct measurement for VPs.

Among all VOAs, not all of these molecules are due to the beverage itself; some substances are released by container components like cork caps, inducing relevant olfactory defects [121]. The so called "cork taint" is the aroma defect due to the presence of haloanisoles desorbed by faulty cork caps; these molecules are produced as byproducts of the whitening process of the raw material used in the manufacturing of closures. Haloanisoles normally range from about a few ng·L^{-1} in defect-free wines to an order of magnitude more for defective beverages, so an enrichment step is crucial for their analysis, and this preconcentration could be boosted in heterogeneous extraction by preliminary derivatizing analytes [122]. Pizarro et al. developed an HS-SPME method using N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA) for the derivatization of haloanisoles and halophenols in wine [123]. This reaction involves one or more active hydrogen atoms from the organic molecule which are replaced by a trialkyl-substituted silyl group. In this method, MSTFA was chosen as a trimethylsilyl (TMS) donor because of its significant volatility, which allows OFD using its vapors [124,125]. The procedure is based on an OFD design which requires a double-step extraction. First, 10 mL of sample were extracted without preliminary treatments using a polyacrylate (PA) extraction fiber at 70 °C for 60 min. After that, the enriched phase was further exposed to 50 µL of MSTFA for 25 min at 25 °C in order to perform the derivatization. The proposed method showed satisfactory linearity, precision, and detection limits for the analysis of red wine samples.

3. Conclusions

Flavor analysis is one of the most important application fields in analytical chemistry and also the most advanced; the quantification of target volatile molecules is crucial, especially for fermented beverages like beer and wine, but it is also a critical task because of matrix complexity and the reduced concentration of analytes. Today's trend is directed towards environmental sustainability, so sample preparation was evolved, minimizing volumes and removing as many steps as possible that involve derivatization. However, when it comes to dealing with highly complex matrices and low concentrations, the derivatization process is still mandatory for some classes of analytes. To date, carboxylic acids, volatile thiols, and carbonyls were the classes of VOAs that still required derivatization and have been considered in this review. For carboxylic acids, the elected technique was silylation via TMS precursors to substitute through an SN2 the hydrophilic function that reduced volatility and interfered with GC analysis. Silylation was also used for some volatile phenols and haloanisoles following the same chemical principles to enhance performance when their concentration became critically low. Based on a similar purpose, in VCCs an oxime was formed by nucleophilic addition to the carbonyl function using a pentafluorobenzylhydroxylamine reactant (PFBHA). It must be underscored that for VCCs in beverages at $\mu g \cdot L^{-1}$, there is still no alternative to HS-SPME and derivatization coupled to GC-MS. Volatile thiols are present in beverages at $ng \cdot L^{-1}$ levels, so derivatization is needed to compensate for this lack against the selected techniques: pentafluorobenzylbromide (PFBBr) was used to substitute the hydrophilic hydrogen and increase the volatility prior to GC as for the carboxylic function in fatty acids. Ebselen was to date the best derivatizing agent in LC-MS protocols because it was used to form selenium-based adducts that had an improved response factor in electrospray ionization. All recent procedures considered are efficient (almost total yield), fast (most required less than 30 min), and compatible with analytical requirements. Thanks to these characteristics, it was possible to further down-scale the procedure and make it compliant with the green analytical chemistry principles.

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Abbreviations

VOAs	volatile odor-active molecules
GC	gas chromatography
LC	liquid chromatography
MS	mass spectrometry
LLE	liquid-liquid extractions
SPE	solid-phase extractions
SPME	solid-phase micro-extraction
OSD	on-solution derivatization
OFD	on-fiber derivatization
SBSE	stir bar sorptive extraction
EI	electron ionization
API	atmospheric pressure ionization sources
APCI	atmospheric pressure chemical ionization
ESI	electrospray ionization
LOD	limit of detection
LOQ	limit of quantitation
ODT	odor detection threshold
VTs	volatile thiols

VSCs	volatile sulphur compounds
VCCs	volatile carbonyl compounds
VPs	volatile phenols
p-HMB	p-hydroxymercuribenzoate
PFBBr	p-entafluorobenzyl bromide
ETP	ethyl propiolate
DTDP	4,4′-dithiodipyridine
ebselen	2-phenyl-1,2-benzisoselenazol-3-one
PFBHA	O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine hydrochloride
DNPH	2,4-dinitrophenylhydrazine
MSTFA	N-methyl-N-(trimethylsilyl) trifluoroacetamide
TMSCN	trimethylsilyl cyanide
NBDI	used O-(4-nitrobenzyl)-N,N′-diisopropylisourea
BSTFA	bis(trimethylsilyl)trifluoroacetamide
TMCS	trimethylchlorosilane
TMS	trimethylsilyl
PA	polyacrylate
PDMS	polydimethylsiloxane
DVB	divinylbenzene
CAR	carboxen

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