Microextraction Techniques in Lipid Peroxidation Product Detection

Subjects: Chemistry, Analytical

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Lipid peroxidation, the most aggressive reaction in food, results in the formation of reactive organic compounds that detrimentally impact food sensory qualities and consumers' health. While controlled lipid peroxidation can enhance flavors and appearance in certain foods, secondary peroxidation products lead to sensory deterioration in a variety of products, such as oils, alcoholic beverages, and meat. Dispersive liquid-liquid microextraction (DLLME), solid-phase microextraction (SPME), and gas-diffusion microextraction (GDME). These techniques offer efficient and sensitive approaches to extracting and quantifying lipid oxidation products and contribute to the understanding of oxidative deterioration in various food products.

food analysis gas-diffusion microextraction lipid peroxidation

dispersive liquid-liquid microextraction solid-phase microextraction

1. Introduction

Lipid peroxidation, autooxidation, or oxidative rancidity, is the most aggressive reaction in food that results in the formation of reactive organic compounds [1]. These compounds have an adverse effect on the sensory qualities of food and can potentially harm consumer health [1][2]. Lipid peroxidation is driven by the complex interaction of polyunsaturated fatty acids (PUFA) with reactive oxygen species (ROS) (**Figure 1**), resembling free radical reactions [3]. Exposure to factors like light, heat, or metallic ions initiates the process by releasing hydrogen atoms, forming radical carbonations. These radicals rearrange to create conjugated systems [1][2][4]. Atmospheric oxygen reacts with these conjugated dienes, generating peroxide radicals that sustain the chain reaction [3][4]. Although lipid peroxides are relatively stable, further degradation occurs through heat or metal ions, resulting in more stable secondary products [3][5]. The extent of autooxidation varies based on factors such as storage conditions, oxygen levels, and lipid composition, with the number of unsaturated bonds in the fatty acid influencing the susceptibility [5][6][7].

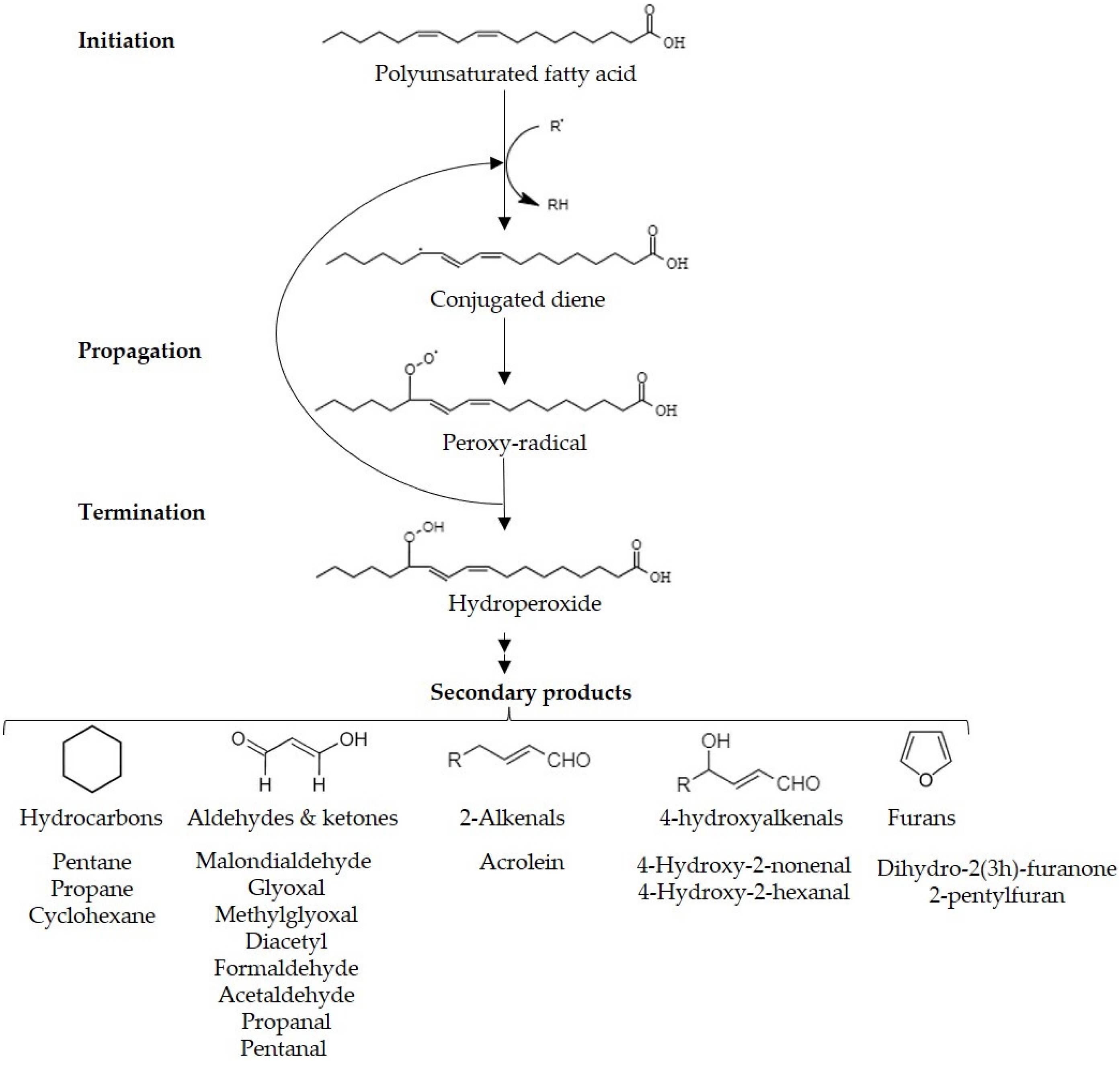

Figure 1. Pathway of lipid peroxidation.

Controlled lipid peroxidation possesses positive effects, enhancing the flavors in certain products like aged cheese, roasted coffee beans, and toasted nuts [8][9]. However, secondary lipid peroxidation products can lead to sensory deterioration and off flavors in various foods, including oils, alcoholic beverages, meat, milk, and dairy products [9][10][11][12][13]. The susceptibility to autooxidation varies among different edible oils, with olive oil's resistance attributed to its high phenolic content [10][14]. Alcoholic beverages, such as wine and beer, can develop lipid peroxidation products due to the interaction of PUFA in the raw materials with lipid peroxidation factors during production and fermentation [15][16]. Yeast metabolism in alcohol fermentation can also contribute to generating ROS, accelerating oxidative rancidity [17]. Extended periods of aging and storage, common in wines, further expose them to oxidative conditions [18]. Meat products, processed through grinding, cutting, and packaging, expose more surface area to ROS, promoting lipid peroxidation, which is exacerbated by extended storage times, especially under improper conditions [12][19]. Additionally, food products made from meat or fish are high in protein, PUFA and monounsaturated fatty acids (MUFA), and salt can experience protein deterioration due to primary (hydroperoxides) and secondary (aldehydes, ketones) lipid oxidation products reacting with free proteins, peptides, and amino acids [12][19].

Excessive lipid peroxidation can have adverse health effects by producing secondary peroxidation products that interact with biomolecules (proteins, peptides, nucleic acids, and other lipids) within cells, potentially leading to toxic and mutagenic effects [1][2][3].

These secondary lipid peroxidation products can follow two pathways: they can break down into carbonyl compounds like aldehydes, ketones, and alcohols [1][2], or undergo cyclization to form malondialdehyde, which can then dehydrate into acrolein [20].

The International Agency for Research on Cancer (IARC) classifies certain secondary peroxidation products based on their potential carcinogenic hazards to humans [21]. This classification (**Table 1**) categorizes compounds according to their level of evidence as carcinogens into different groups: **Category 1**, indicating *sufficient evidence of its carcinogenicity to humans*, **Category 2A**, suggesting they are *probably carcinogenic to humans* based on limited evidence. **Category 2B**, indicating that they are *possibly carcinogenic to humans*, supported by limited evidence, and **Category 3**, indicating *insufficient evidence for their carcinogenicity*.

Table 1. Classification of secondary lipid peroxidation products based on their carcinogenetic and recommended exposure levels.

Secondary Product		CAS Number	IARC Category	Tolerable Daily Intake µg/Kg bw/Day	Reference
Saturate Carbonyls	Formaldehyde	50-00-0	1	150	[22]
	Acetaldehyde	75-07-0	2B	185 ^{a}	[23]
	Hexanal	66-25-1	-	780 *	[24]
α,β-Unsaturated Carbonyls	Acrolein	107-02-8	2A	7.5	[25]
	4-hydroxy-2-nonenal	75899-68-2	3	1.5 **	[26]
	4-hydroxy-2-hexenal	17427-21-3	3	1.5 **	[26]
	Acrylamide	79-06-1	2A	NE	[27]

Secondary Product		CAS Number	IARC Category	Tolerable Daily Intake µg/Kg bw/Day	Reference
Dicarbonyls	Crotonaldehyde	4170-30-3	2B	-	-
	Malondialdehyde	102-52-3	3	30 **	[26]
	Glyoxal	107-22-2	-	200	[28]
	Methylglyoxal	78-98-8	3	-	-
	Diacetyl	431-03	-	900 *	[28]
Furans	Dihydro-2(3H)-furanone	96-48-0	3	-	-
	Furfural	98-01-1	3	500	[29]

[26][27][28][29][30] based on

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IARC, International Agency for Research on Cancer; bw, body weight; ª Acceptable intake reported as µg/day; * Acceptable daily intake; ** Threshold of toxicological concern set by The International Programme on Chemical Safety (IPCS); NE, non-established.

Quantifying primary peroxidation products is challenging due to their reactivity and volatility [32]. Therefore, the measurement of secondary lipid peroxidation products is commonly used as biomarkers to monitor oxidative stress within cells [33]. Additionally, these products can serve as markers of food quality to assess the oxidative state of food products [34]. Various analytical techniques have emerged in recent years for analyzing and quantifying carbonyl compounds, with applications in food, biological, and environmental studies [33][35]. These methods primarily involve spectrometry and chromatography technologies [35]. A direct measurement of carbonyl compounds offers non-destructive and specific approaches, minimizing sample contamination risks due to their natural occurrence [35][36][37][38]. Direct methods for carbonyl compound analyses in food mainly employ flame ionization detectors (FID) and electron capture detectors (ECD). However, they may have increased detection limits due to potential analyte degradation within the detector [36][37][38]. In contrast, indirect methods offer a way to detect secondary peroxidation products by forming carbonyl adducts, which are determined using ultraviolet (UV), fluorescence (FLD), and mass spectrometry (MS) [10][39][40][41][42][43].

The traditional thiobarbituric acid (TBA) reactive substances (TBARS) assay has been employed to determine carbonyl compounds as lipid peroxidation products in biological and food samples [39]. This assay involves the reaction with TBA to form a chromophore detectable by spectrophotometric methods [39][43]. However, TBARS lack specificity due to interactions with various organic compounds [39]. Therefore, some applications incorporate a separation step, often via liquid chromatography (LC), before determination [43]. Other derivatization reagents, such as hydrazines, react with carbonyl compounds to form hydrazones, detectable spectroscopically after LC or gas chromatography-mass spectrometry (GC-MS) [40][41][42]. Phenyl hydrazine (PH) and derivatives such as 2,4-Dinitrophenylhydrazine (DNPH) and 2,3,4,5,6-pentafluorophenylhydrazine (PFPH) are commonly used for this purpose [40][41][42].

The choice of a sample preparation method depends on various factors, including the sample's state (solid, liquid, gas), size, the analytical technique used, the type of analysis, properties of the analyte, and its initial concentration [44]. Traditional sample preparation methods often involve significant quantities of organic solvents, multiple steps, and result in substantial waste and time consumption [45]. An ideal sample preparation method should be simple, time efficient, cost effective, rugged, potentially automated, and align with the principles of *green analytical* *chemistry,* with a focus on minimizing sample, solvent, and waste usage [44][45]. Furthermore, simultaneous derivatization and extraction can reduce the overall analysis time while enhancing sensitivity and specificity [46]. In response to these needs, novel microextraction-based methods have emerged. Microextraction involves using a small volume of an extracting phase compared to the sample volume [47][48][49][50]. While it may not achieve exhaustive extraction, it significantly increases the concentration of the analyte in the extractive phase, reducing solvent usage [47][48][49][50]. The efficiency of microextraction depends on how the analyte partitions between the matrix and the extractive phase [51]. Since partitioning is not affected by analyte concentration, quantification is based on the absolute amount extracted [52]. The affinity of the analyte for the extraction phase determines the quantity extracted [51][52]. Moreover, microextraction operates on equilibrium, where extraction time determines the system's equilibrium position [53]. Once equilibrium is reached, no further analyte extraction occurs [51][52][53]. Microextraction can also serve as a pre-concentration step before analysis [49][50][51].

Microextraction techniques, including dispersive liquid-liquid microextraction (DLLME), solid-phase microextraction (SPME), and gas-diffusion microextraction (GDME), have gained prominence in the analysis of lipid peroxidation in food. These techniques provide efficient and sensitive approaches to extracting and quantifying lipid oxidation products, thereby contributing to understanding the oxidative deterioration of food products.

2. Gas Diffusion Microextraction

GDME (**Figure 2**) was introduced to the scientific community through the Journal of Separation Science in 2010 [48].

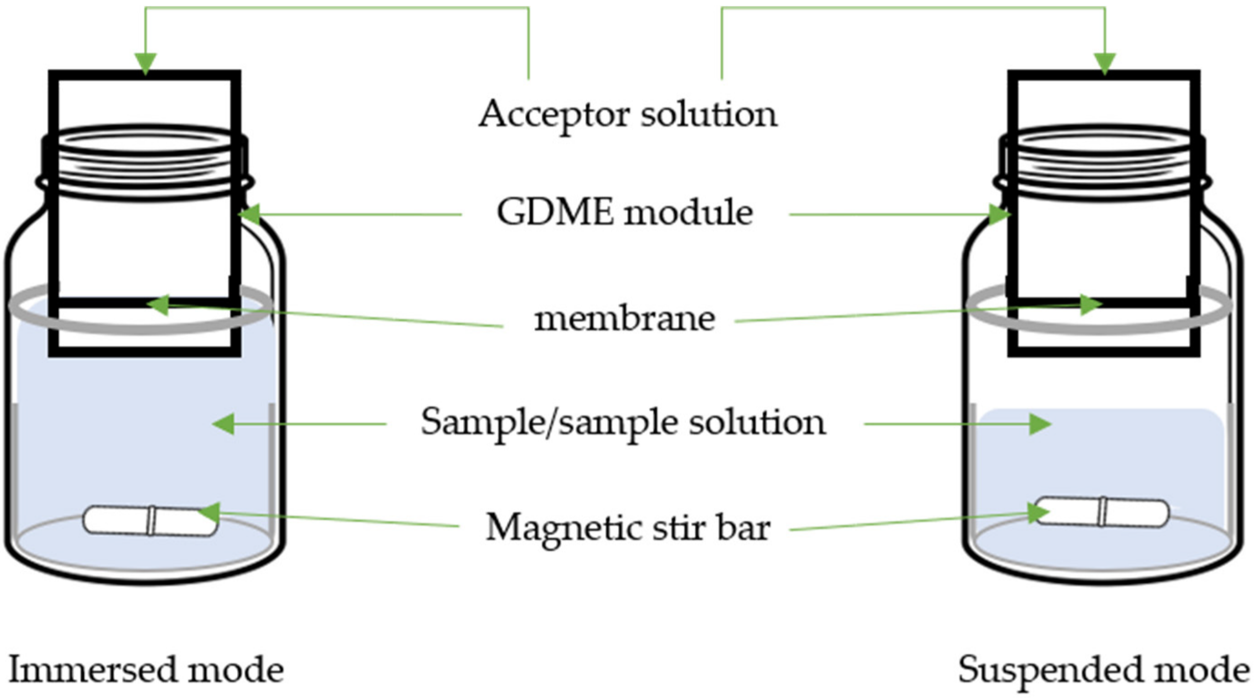

Figure 2. Scheme of gas-diffusion microextraction (GDME).

GDME is a versatile and efficient technique offering several advantages in addressing food matrices complexities. Its selective extraction capability allows the isolation of specific target compounds from complex mixtures, ensuring precise analysis even in interfering components. GDME operates through passive diffusion, with target compounds migrating from the sample matrix into an acceptor phase, usually a liquid solution containing a derivative reagent. This process involves placing the acceptor phase in the GDME module containing a microporous hydrophobic membrane, typically a 5.0 µm PTFE membrane, which supports the acceptor phase. Equilibrium is established between the sample and acceptor phases, and the acceptor phase is collected for analysis. GDME's minimal sample requirements make it well suited for limited availability, while its reduced solvent usage aligns with the trend of *green analytical chemistry* [45]. GDME exhibits high sensitivity, when coupled with sensitive detection methods like GC-MS or high-performance liquid chromatography-ultraviolet (HPLC-UV). This empowers the quantification of trace-level compounds in food analyses [10][48][54][55][56][57][58][59][60][61][62].

From quality control to monitoring changes during storage and processing, GDME's synergy with analytical techniques such as GC and HPLC unveils the intricacies of food composition and quality, setting its status as an indispensable tool in modern food analysis practices. Its selective enrichment capabilities enhance the detectability of compounds, making GDME valuable for trace analysis. In practice, GDME is employed for discerning volatile aroma compounds, evaluating off flavors, assessing lipid oxidation products, and analyzing a spectrum of other volatile constituents. Additionally, GDME's non-destructive nature preserves the integrity of samples for further investigations, enhancing the versatility of its applications across various food products, including solid (bread and coffee beans), liquid (beer, wine, soy sauce), and semi-liquid (vegetable oils) foods. **Table 2** presents a comparison of the methods developed for the analysis of carbonyl compounds using GDME.

Table 2. Analytical method for determination of secondary peroxidation products by gas-diffusion microextraction (GDME).

Target Compound	**Sample**	**GDME**				**Derivative Reagent**	**Determination**	**LOD µg/L or µg/Kg**	**Recovery %**	**Ref.**
		Mode	**$V_{\text{acceptor solution}}$ mL**	**t min**	**T °C**					
1,3-pentadione Diacetyl	Beer	Immersed	0.5	15	40	*O*-PDA	HPLC-UV	3.8–4.6	-	[48]
2 aldehydes & Furfural	Beer	Immersed	0.75	5	30	DNPH	HPLC-UV	1.5–12.3	-	[54]
5 aldehydes	Beer	Suspended	0.5	20	40	HBA	HPLC-DAD	1.2–1857.7	>96%	[55]
Diacetyl [1]	Wine	Immersed	0.4	20	65	O-PDA	HPLC-UV	3.8	-	[56]
Acetaldehyde [1]	Wine	Immersed	1.0	15	50	DNPH	HPLC-UV	800–1100	-	[57]

Target Compound	Sample	GDME				Derivative Reagent	Determination	LOD µg/L or µg/Kg	Recovery %	Ref.
		Mode	$V_{acceptor\ solution}$ mL	t min	T °C					
Diacetyl	Wine & beer	Suspended	1.0	10	60	*O*-PDA	DPV	0.053	-	[58]
α-DCC	Wine; black tea & soy sauce	Immersed ^{2}	0.5	10	55	*O*-PDA	HPLC-UV	50–200	-	[59]
MDA	Vegetable oil	Suspended	0.5	30	65	TBA	HPLC-UV/FLD	250–350	≥82%	[60]
4 aldehydes Acrolein & MDA	Vegetable oil	Suspended	1.0	10	60	DPNH	GC-MS	50–100	≥95%	[10]
2 ketones & diacetyl	Ground bread	Suspended	0.5	15	65	*O*-PDA	HPLC-UV	6–12	-	[61]
27 carbonyl compounds ^{3}	Green & roast coffee beans	Suspended	0.5	16	40	*O*-PDA	HPLC-DAD	50–200	-	[62]

[1] free and total; [2] 0.22 µm PVDF membrane; [3] Qualitative analysis; LOD, limit of detection; Ref., reference; DNPH, 2,4-dinitrophenylhydrazine; HBA, 4-hydrazinobenzoic acid; *O*-PDA, *O*-phenylenediamine; α-DCC, α-dicarbonyl compounds; MDA, malondialdehyde; TBA, 2-thiobarbituric acid; DPV, differential pulse voltammetry.

3. Solid-Phase Microextraction

SPME (Figure 3) is a well-established sample preparation technique commonly used in analytical chemistry to extract and concentrate target compounds from various sample matrices before analysis [49][51][63].

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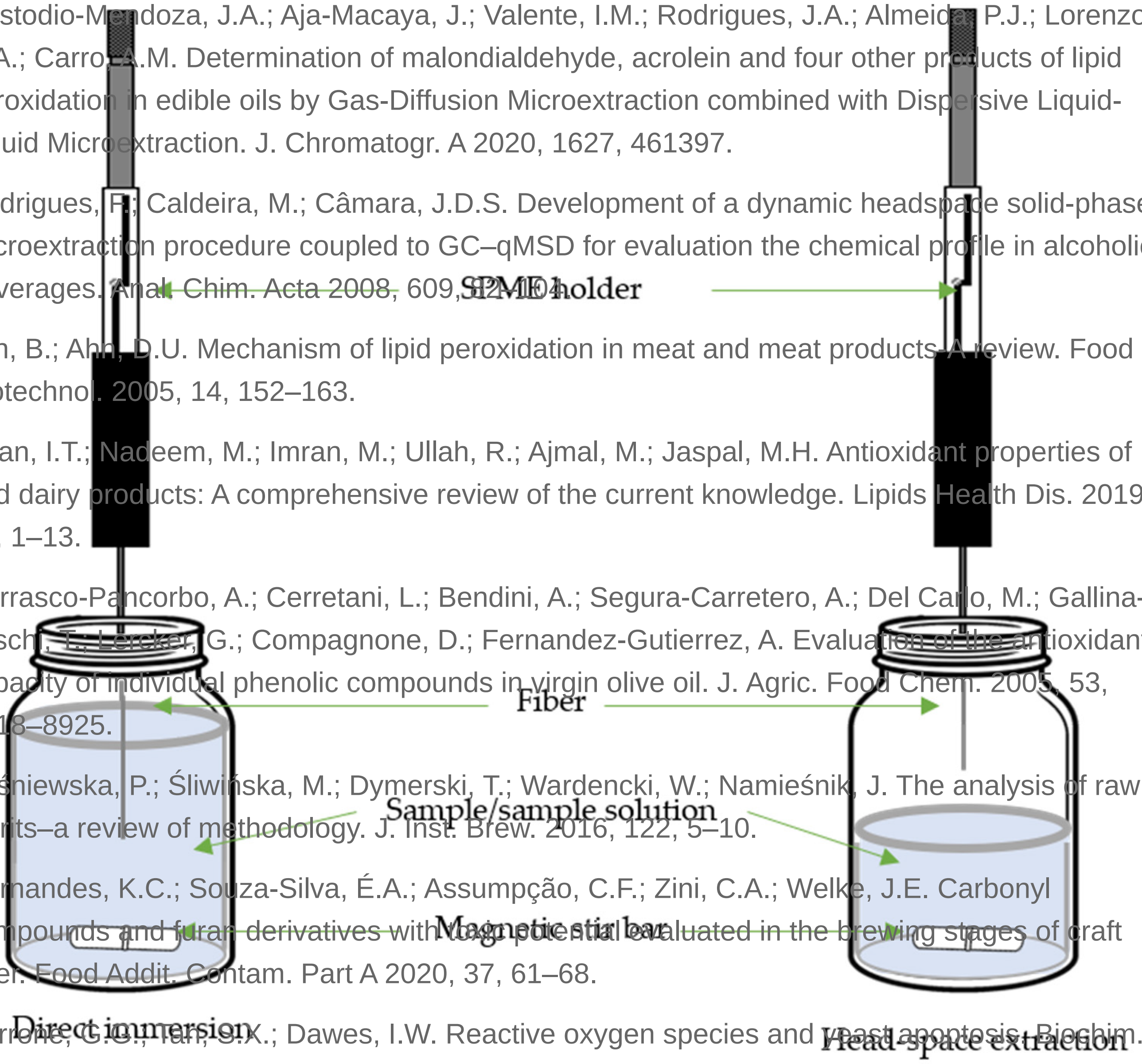

Figure 3. Scheme of solid-phase microextraction (SPME).

SPME finds particular utility in extracting volatile and semi-volatile compounds from complex matrices, especially in food analysis. SPME involves a fiber coated with a thin layer of an absorbent material, which is exposed to the sample to extract the analytes of interest [49][68]. The SPME process comprises several key steps: *equilibration*, when the SPME fiber is exposed to the sample (either in immersed mode or sample headspace) to allow analytes to partition between the sample matrix and the fiber coating, *adsorption*, when the analytes are absorbed onto the fiber coating, concentrating them from the sample matrix, and *desorption* of the analytes from the fiber coating to the analytical instrument for analysis [63].

The application of SPME for analyzing lipid peroxidation products is well justified due to its selective extraction capabilities, which minimize interference from complex matrices. SPME simplifies sample preparation by concentrating trace amounts of these compounds, enhancing sensitivity, and eliminating the need for extensive cleanup steps [49][63]. Furthermore, its reduced solvent usage aligns with environmental concerns [63]. SPME's

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adaptability to various sample types enables real-time monitoring and preparation for studying lipid peroxidation in biological, food, and other samples [49][63]. Its compatibility with quantitative and qualitative analytical techniques, coupled with its ability to mitigate matrix effects, further underlines its value as a technique for accurate and comprehensive lipid peroxidation product analysis (**Table 3**).

Table 3. Analytical methods for determination of secondary peroxidation products by solid-phase microextraction (SPME).

Target Compound	Sample	SPME					Derivative Reagent	Determination	LOD µg/L or µg/Kg	Recovery %	Ref.
		Mode	t min	T °C	Fiber	$T_{desorption}$ °C					
14 aldehydes & ketones	Vegetable oil	HS	30	20	DVB/CAR/PDMS	270	-	GC-FID & GC-MS	0.04–2.24	-	[64]
4-HNE	Oils & porcine liver	DI	15	40	PDMS/DVB		DNPH	HPLC-SP	0.001–1.42	66–87%	[65]
MDA	Cod liver oil	HS	10	RT	PDMS/DVB	200	N-MH	GC-NPD	0.74	91%	[66]
Hexanal	Hazelnut	HS	10	60	CAR/PDMS	300	-	GC-FID	8.01	-	[67]
7 aldehydes	Peanut, soybean and olive oils	HS	15	50	CAR/PDMS	250	-	GC-FID	4.6–10.2	85–110	[68]
3 α,β-UC	Sunflower oil digestion phases	HS	60	50	DVB/CAR/PDMS	250	-	GC-MS	-	-	[69]
100 carbonyl compounds	Cod liver oil	HS	60	50	DVB/CAR/PDMS	220	-	GC-MS	-	-	[70]
18 VOC	Sunflower oil emulsions	HS	30	50	DVB/CAR/PDMS	250	-	GC-MS	-	-	[71]
Aldehydes & 2-pentylfuran	Soybean oils	HS	55	50	DVB/CAR/PDMS	250	-	GC-MS	-	-	[72]
VOC	Peanut oil	HS	40	50	PDMS/DVB	250	-	GC-MS	-	-	[73]
4 aldehydes	Roast & boiled duck	HS	40	45	CAR/PDMS	280	-	GC-MS	-	-	[74]

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Target Compound	Sample	SPME					Derivative Reagent	Determination	LOD μg/L or μg/Kg	Recovery %	Ref.
		Mode	t min	T °C	Fiber	$T_{desorption}$ °C					
& 1 ketone											
3 aldehydes	Chicken patties	HS	10	60	DVB/CAR/PDMS	250	-	GC-FID	-	-	[75]
Hexanal	Pig sausages	HS	30	50	DVB/CAR/PDMS	220	-	GC-MS	-	-	[76]
2 aldehydes & 2 dialdehydes	Cod	HS	30	50	CAR/PDMS	260	-	GC-FID	-	-	[77]
8 aldehydes	Fish	HS	15	60	PDMS/DVB	260	PFBHA	GC-MS	1.4–6.1	79–102	[78]
6 aldehydes	Caviar	HS	30	60	DVB/CAR/PDMS	250	-	GC-MS	-	-	[79]
198 VOCs	Dry cured meat	HS	30	37		260	-	GC-MS	-	-	[80]
Aldehydes	Infant formula	HS	10	25	PDMS/DVB	250	-	GC-MS	-	-	[81]
3 aldehydes & pentane	Infant formula	HS	45	37	CAR/PDMS	250	-	GC-FID	0.02–1.05	-	[82]
13 Carbonyl compounds	Milk powder	HS	45	43		250	-	GC-MS	2–6	-	[83]
VOC	Smoked cheese	HS	45	50	CAR/PDMS	260	-	GC-MS	-	-	[84]
VOC	Mozzarella	HS	15	37		220	-	GC-MS	-	-	[85]
VOC	Portuguese cheese	HS	45	50	DVB/PDMS	250	-	GC-MS	-	-	[86]
9 aldehydes	Beer	HS	60	50	PDMS/DVB	250	PFBHA *	GC-MS	-	89–114	[87]
41 carbonyl compounds	Beer	HS	40	60	PDMS/DVB	250	PFBHA *,**	GC-MS	0.003–20,000	-	[88]
250 carbonyl	Beer	HS	20	45	PDMS/DVB	250	PFBAH **	GC-ITMS	0.003–0.510	88–114	[89]

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Target Compound	Sample	SPME					Derivative Reagent	Determination	LOD µg/L or µg/Kg	Recovery %	Ref.
		Mode	t min	T °C	Fiber	$T_{desorption}$ °C					
compounds											
6 carbonyl compound	Beer	HS	60	55	DVB/CAR/PDMS	250	TFEH **	GC-MS	0.03–0.5	90–105	[16]
6 carbonyl compound	Craft beer	HS	60	55	DVB/CAR/PDMS	250	TFEH **	GC-MS	0.03–0.5	90–105	[90]
18 carbonyl compound	Wine	HS	45	40	DVB/CAR/PDMS	250	-	GC-ITMS	0.62–129.2	19–190	[91]
80 VOC	Wine	HS	30	40	DVB/CAR/PDMS	240	-	GC-MS	-	-	[92]
6 carbonyl compound	Syrah wines	HS	45	55	DVB/CAR/PDMS	250	TFEH	GCxGC-TOFMS	0.5–5.2	90–106	[93]
3 aldehydes	Must & wine	HS	45	55	DVB/CAR/PDMS	250	TFEH	GC-qMS	0.1–0.8	90–102	[94]
38 carbonyl compound	Port wine	HS	20	32	PDMS/DVB	250	PFBHA	GC-MS	0.006–0.089	88–119	[95]
45 carbonyl compound	Wine	HS	20	40	PDMS/DVB	250	PFBHA	GC-MS/MS	-	71–146	[96]
9 aldehydes	Spirits and alcoholic beverages	DI	15	20	PDMS	250	PFBHA	GC-ECD	0.05–0.5	-	[97]
VOC & SVOC	Beer, wine & whisky	HS	60	30	PDMS CAR/PDMS DVB/CAR/PDMS	250 260 260	-	GC-MS	-	-	[11]
20 aldehydes	Green pomace distillates	HS	40	55	PDMS/DVB	250	PFBHA	GC-MS	0.0007–0.02	76–110	[98]
107 VOC	Cider	HS	30	50	DVB/CAR/PDMS	250	-	GC-MS	-	-	[99]
53 carbonyl compounds	*Huangjiu* (alcoholic beverage)	HS	35	45	DVB/CAR/PDMS	250	*PFBHA*	GC-MS/MS	-	71–146	[100]
2 α-DCC	Soybean paste, red pepper past, soy sauce, wine, beer,	HS	20	85	DVB/CAR/PDMS	240	*TFEH*	GC-MS	0.7–1.1	92–104	[101]

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Target Compound	Sample	SPME					Derivative Reagent	Determination	LOD µg/L or µg/Kg	Recovery %	Ref.
		Mode	t min	T °C	Fiber	$T_{desorption}$ °C					
	distilled liquor										

LOD, zene;
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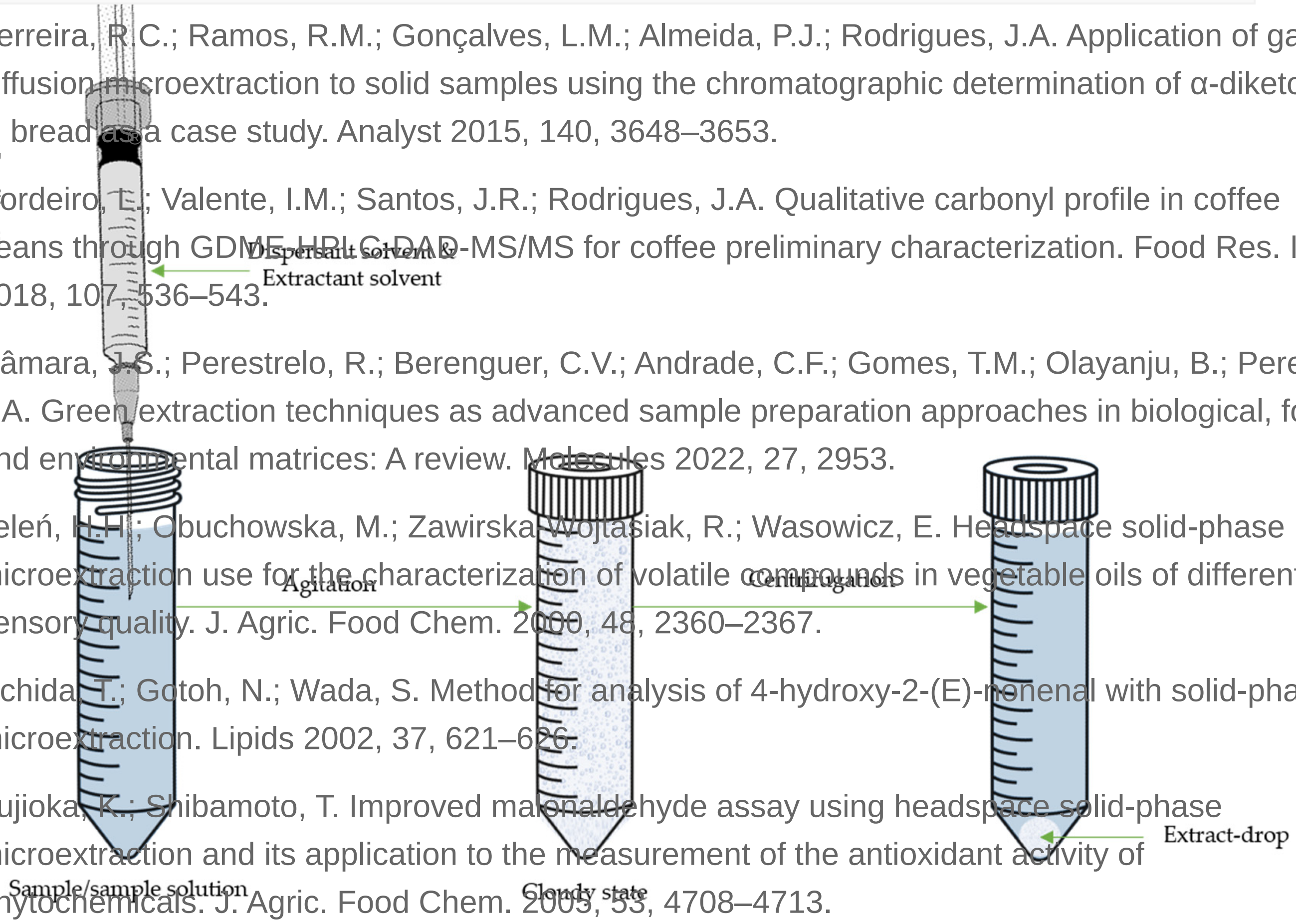

Figure 4. Scheme of dispersive liquid–liquid microextraction (DLLME).

DLLME is characterized by its simplicity, speed, efficiency, and capacity for high enrichment due to the high proportion of donor and acceptor phases. Therefore, the most important parameters of DLLME are the selection of extraction conditions and the choice of dispersive solvents for analytes extraction. An appropriate dispersive solvent must be miscible with the extraction phase and the aqueous phase to create fine droplets in the sample matrices, thus enhancing the interaction between the two phases, resulting in high extraction efficiency.

The most commonly used dispersing solvents are acetone, acetonitrile, and short-chain alcohols (such as methanol, ethanol, and propanol) [105]. The extracting solvent must possess higher density than water, high extraction capacity, and good chromatographic behavior. In classical DLLME, chlorinated solvents such as chloroform, carbon tetrachloride, chlorobenzene, or dichloromethane are the most commonly used extractive solvents. However, these solvents are toxic and harmful to the environment. Over recent years, DLLME has evolved, utilizing less toxic extracting solvents, such as ionic liquids (IL) or less dense extractant solvents than the aqueous phase, such as alcohols [104][105][106]. Ionic liquids (IL) exhibit unique properties, including negligible vapor pressure, miscibility with water and organic solvents, good solubility for organic and inorganic compounds, high

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temperature stability, and respect for the environment. Additionally, they efficiently absorb and transfer microwave energy and are formed by a central molecule that combines organic cations and several anions [106][107].

Furthermore, DLLME can be coupled in a single step of in situ derivatization and extraction of analytes of interest and even combined with other extraction techniques, such as GDME or ultrasound-assisted extraction (UAE). Table 4 presents a comparison of the methods developed for the analysis of secondary peroxidation products using DLLME.

Table 4. Analytical method for determination of secondary peroxidation products by dispersive liquid-liquid microextraction (DLLME).

Target Compound	Sample	DLLME					Derivative Reagent	Determ.	LOD µg/L or µg/Kg	Rec. %	Ref.
		Mode	Disperser	Extracting Solvent	T min	T °C					
Formaldehyde	Beverages	MW-IL-	ACN	IL 3453W	1.5	-	DNPH	HPLC-UV	0.12	85–95	[108]
Acrylamide	Brewed coffee	-	ACN	DCM	-	-	-	UPLC-MS/MS	900	97–106	[109]
PCB and acrylamide	Milk/Coffee	IL	[HeOHMIM][Cl]	[BMIM][NTf2]	-	-	-	HS-GC-ECD-MS	-	-	[110]
MDA, acrolein, 4-HNE	Beverages	US	ACN	CH_3Cl	5	60 °C	DNPH	GC-MS	50–200	94–102	[111]
Formaldehyde	Milk	IL	MeOH	IL 3453W	0.75	45 °C	ACAC	UV	100	91–103	[112]
Acrylamide	Coffee, chocolate, roasted nuts, French fries, cereals, biscuits, chips, bread, and caramelized fruit	SSA	SUPRAS-2 (SDS/TBABr/AlCl3)		2		-	UV	0.2	93–96	[113]
Acrylamide	Nuts and seeds	-	PCE	EtOH	3	-	Xanthydrol	GC-MS	0.6	95	[114]

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Target Compound	Sample	DLLME					Derivative Reagent	Determ.	LOD µg/L or µg/Kg	Rec. %	Ref.
		Mode	Disperser	Extracting Solvent	T min	T °C					
Acrylamide	Potato chips	UAE	PCE	EtOH	2	-	Xanthydrol	GC-MS	0.6	97	[115]
Acrylamide	Cereal products	-	PCE	EtOH	1	-	Xanthydrol	GC-MS	0.6	95	[116]
Acrylamide	Bread	UAE	PCE	MeOH	1	-	Xanthydrol	GC-MS	0.54	98	[117]
4 aldehydes Acrolein & MDA	Vegetable oil	US	ACN	CH_3Cl	5	60	DPNH	GC-MS	50–100	≥95%	10

LOD, limit of detection; Determ., determination; Rec., recovery; Ref., reference; MW, Microwave; IL, Ionic liquid; IL 3453W, Trihexyltetradecylphosphonium Chloride; DNPH, 2,4-dinitrophenylhydrazine; DCM, Dichloromethane; PCB, polychlorinated biphenyls; MDA, malondialdehyde; US, Ultrasound; UAE, ultrasound-assisted extraction; PCE, tetrachloroethylene; SSA, supramolecular solvent-assisted; ACAC, acetylacetone in an ammonium acetate (2.0% *v/v*).

5. Combined Microextraction Techniques

Recent advancements in analytical sample preparation reflect a growing trend of integrating diverse extraction techniques to enhance aspects such as separation, cleanup, detection limits, enrichment factors, and the handling of complex sample matrices. The combination of microextraction methods to assess both organic and inorganic targets has proven valuable within the realm of modern analytical chemistry [118]. This approach allows for the concurrent execution of target extraction, pre-concentration, and cleanup stages, effectively shortening the overall procedure time and aligning well with the principles of green analytical chemistry [45][46][47]. This trend underscores a significant progression in analytical sample preparation, harnessing the strengths of various techniques to address intricate analytical challenges and yielding enhanced accuracy, sensitivity, and efficiency in analyzing a wide range of samples [119].

Custodio-Mendoza and colleagues introduced a novel approach involving simultaneous GC-MS analysis of MDA, acrolein (ACRL), formaldehyde, acetaldehyde, propanal, and pentanal, utilizing suspended GDME combined with DLLME [10]. The requirement for analytes to be in a suitable non-polar organic solvent for GC-MS analysis posed limitations on GDME's application. This challenge became particularly pronounced for carbonyl compounds, especially when derivatized, due to their high volatility, making solvent exchanges intricate.

To address this, Custodio-Mendoza et al. employed a multi-step strategy. They commenced with GDME under optimized conditions: a 10 min extraction at 60 °C using 1 mL of DNPH (0.5 g/L in 2 M HCl) solution as the

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acceptor phase. The innovation emerged in the subsequent steps. The acceptor phase, containing aldehyde-DNPH derivatives, was transferred to a tube containing 4 mL of ultrapure water to undergo DLLME. A mixture of acetonitrile (0.75 mL) and 70 μL chloroform was injected into the aqueous phase and subjected to sonication at 60 °C for 5 min. This combination of techniques resulted in a cleaner extract with enhanced selectivity and sensitivity. Various solvents including isooctane, hexane, and chloroform were evaluated for optimal extraction.

Remarkably, DLLME facilitated solvent exchange and amplified method sensitivity through enrichment factors, significantly lowering detection limits and enhancing result precision. Another distinctive aspect of their approach was incorporating ultrasonic agitation during the SDME process, which substantially reduced extraction time, optimizing method efficiency and cost-effectiveness. This advancement not only surmounted a significant analytical challenge but also refined sensitivity and analysis speed. The processing and storage of edible oils can lead to oxidation, generating volatile compounds like hydrocarbons, aldehydes, alcohols, and ketones. Thus, quantifying these products serves as potential markers for food quality in the oxidative state. Notably, the method was successfully applied to the quantification of forty-eight samples of vegetable oil, spanning categories such as extra virgin olive oil, refined olive oil, olive-pomace oil, and refined seed oil. The outcomes revealed the presence of acrolein and propanal across all samples, with the highest concentration found in one category. Moreover, malondialdehyde levels seemed to decrease in oils enriched with antioxidants or virgin oils. This comprehensive approach demonstrated the potential for robust lipid peroxidation assessment in various oil types.

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