Review

The role of 5-hydroxymethylfurfural in food and recent advances in analytical methods

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ABSTRACT

The thermal processing, storage, and transportation of foodstuffs (e.g., fruit juices, coffee, honey, and vinegar) generate 5-hydroxymethylfurfural (HMF). The food industry uses this compound as a quality marker, thus increasing the demand for fast and reliable analytical methods for its determination. This review focuses on the formation of HMF in food, its desirable and toxic effects, and recent advances in analytical methods for its determination in foodstuffs. The advantages and limitations of these analytical approaches are discussed relative to the main analytical features.

1. Introduction

The changes in human lifestyle have promoted modifications in industrial processing, storage, and transportation of foodstuffs. Thermal treatment is one of the most common processes in the food industry, as it guarantees food safety and improves the quality and shelf life of foodstuffs. In addition, roasting, frying, toasting, and baking change sensory properties (smell, color, taste, and flavor) of foodstuffs and improve consumer acceptability (Belitz, Groch, & Schieberle, 2009; Damodaran & Parkin, 2017). The Maillard reaction and caramelization, involved in these treatments, also produce furfural and its derivatives, including 5-hydroxymethylfurfural (5-(hydroxymethyl)furan-2-carbaldehyde, HMF).

HMF is highly soluble in water and a volatile species (melting and boiling points of 31.5 °C and 115 °C, respectively) and shows maximum radiation absorption at 284 nm. Its generation and/or degradation directly depends on the pH, temperature, and composition of the foodstuffs. Hence the food industry has used HMF as a quality marker and adulteration indicator in specific foods, such as coffee, juices, milk, sauces, honey, and cereals (Damodaran & Parkin, 2017; Lee et al., 2019). Other industrial application refers to the use of HMF for production of fuels, drugs, solvents, and biopolymers (Lee et al., 2019).

Recent toxicological studies demonstrate that ingesting high concentrations of HMF from foodstuffs can adversely affect human health,

such as irritation of the mucous membranes, skin, upper respiratory system, and eyes, as well as neurodegenerative, diabetes, and cardiovascular diseases. Moreover, HMF can be converted into various compounds, such as chloromethylfurfural, sulfoxymethylfurfural, and formic acid, whose ingestion has adverse effects, including mutagenicity (Capuano & Fogliano, 2011; Lee et al., 2019; Stadler & Lineback, 2008). Hence, the HMF acute oral LD_{50} is estimated to be $2.5 - 5.0$ mg kg^{-1} and 2.5 mg kg^{-1} for female and male rats, respectively (Barrera et al., 2021; Deshpande, 2002; Lee et al., 2019; Prata et al., 2021).

Because of the previously mentioned aspects, food industries and regulatory agencies monitor the HMF concentration to ensure adequate processing and identify non-conformities in foodstuffs (Capuano & Fogliano, 2011; ECHA, 2021; FAO/WHO, 2019; Lee et al., 2019). This review aims to discuss the formation of HMF, its beneficial and adverse effects, and some alternatives for control of its concentration on foodstuffs. The main analytical methods for HMF determination are also discussed, highlighting advantages, disadvantages, and perspectives.

2. Formation of HMF

The two main pathways for HMF formation involve either the Maillard reaction, via decomposition of 3-deoxyglucosone, or caramelization, via dehydration of sugars (Capuano & Fogliano, 2011), as presented in Fig. 1. Via the Maillard reaction, reducing sugars (e.g.,

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fructose and glucose), and amino acids produce a Schiff base that forms Amadori and Heyns rearrangement products via cyclization. These compounds are highly unstable and degrade in 1,2-eneaminnol or 1-amino-1-deoxyketose depending on the pH values, which should be 7.0 or lower. The formation of HMF is directly related to the concentration of 1,2-eneaminnol, which produces 3-deoxyglucosone, and is the key intermediate in HMF generation from the dehydration of 3,4-dideoxyglucosone (Belitz, Groch, & Schieberle, 2009; Capuano & Fogliano, 2011; Damodaran & Parkin, 2017; Portillo Perez, Mukherjee, & Dumont, 2019).

The exposure of sugars to thermal treatment under acidic conditions yields fructofuranosyl cations through the acid-catalyzed degradation of fructose, mainly in dry systems. This reaction is called caramelization and occurs typically at temperatures ranging from 150 to 200 °C (Belitz, Groch, & Schieberle, 2009; Capuano & Fogliano, 2011; Damodaran & Parkin, 2017; Portillo Perez, Mukherjee, & Dumont, 2019).

The efficiency of HMF formation is directly influenced by water activity, cation and amino acid concentrations, sugar type, temperature, and pH of the medium (Gökmen & Morales, 2014). Conditions favoring HMF formation include an acidic medium, high fructose concentration, and presence of sodium chloride and calcium. Whereas, high water activity decreases the formation of HMF by inhibiting sugar dehydration. The effect of temperature on the rate of HMF formation was also discussed (Damodaran & Parkin, 2017; Lee et al., 2019; Gökmen and Morales, 2014).

Because of its chemical structure, with a furan ring with aldehyde groups and hydroxyls, HMF has been widely employed in chemical industries (Kucherov et al., 2018). Industrial processes are based on HMF produced from carbohydrate biomass, by exploiting e.g. glucose, fructose, cellulose, and sucrose as substract by means of dehydration reaction. Recent studies have employed cellulose and ionic liquids as environmentally friendly catalysts in the HMF formation reaction (Portillo Perez et al., 2019; Zhang et al., 2020; Zhao et al., 2021). Besides reducing the reaction time, catalytic systems can improve selectivity, minimize costs, and increase the reaction yield (Cai et al., 2022; Capuano & Fogliano, 2011; Portillo Perez et al., 2019).
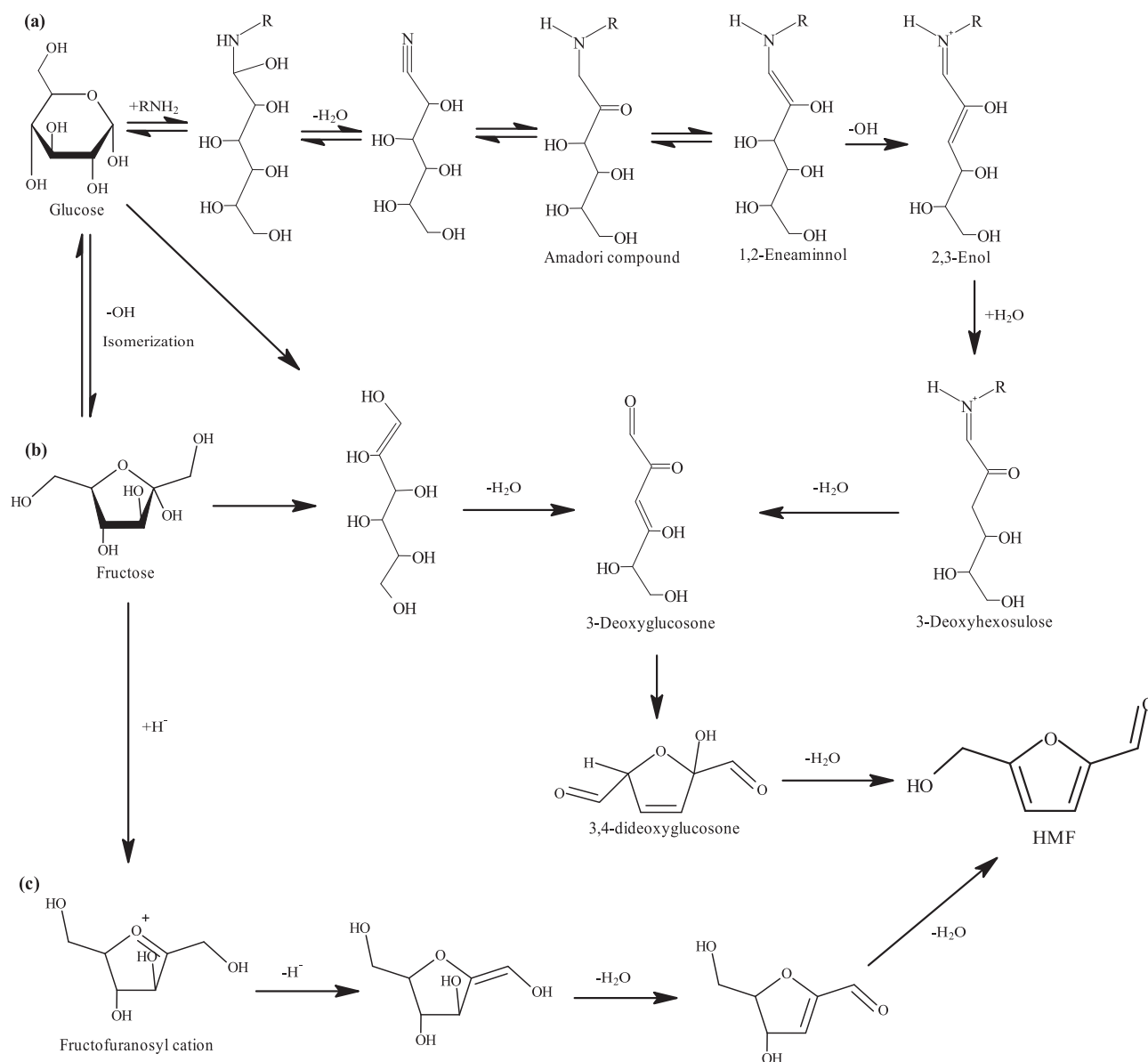
Fig. 1. Reaction schemes of the formation of HMF via Maillard reaction from glucose (a) and fructose (b) or caramelization from frutofuronosyl cation (c). Adapted from (Capuano & Fogliano, 2011; Damodaran & Parkin, 2017; Portillo Perez, Mukherjee, & Dumont, 2019).

3. Applications in foodstuffs

Because the HMF concentration increases during thermal processing or storage time of foods, it has been found in various foodstuffs, such as coffee, milk, juices, honey, cereal products, vinegar, processed fruits, beer, wine, soy sauce, and malt (Apriceno et al., 2018; Barrera et al., 2021; Francisquini et al., 2018). Table 1 shows the HMF concentrations in some foodstuffs as reported in recent studies.

HMF is also related to the composition of foods and carbohydrates are precursor molecules involved in its formation (Capuano & Fogliano, 2011). Vegetables and fruits produce high amounts of HMF owing to sugars and amino acids in their composition. Low concentrations of HMF are found in honey and juice, but the amount increases via adulteration, moisture reduction, long storage time, and inadequate thermal processing, which is performed to prevent undesirable reactions or crystallization (Chen et al., 2019; Lee et al., 2019; Marsol-Vall et al., 2016; Martysiak-Zurowska & Borowicz, 2009).

Although HMF is usually found in low concentrations in cereals and flours, the Maillard and caramelization reactions during the roasting of bakery products significantly increase its concentration. The production

Table 1
Concentration ranges of HMF in some foodstuffs.

Sample	Concentration (mg kg^{-1} or mg L^{-1})	Analytical technique	Reference
Baby foods	0.01 – 343	HPLC-DAD	(Prata et al., 2021)
Beer	4.3 – 7.0	HPLC-DAD	(Viegas et al., 2018)
Black garlic	1880 – 4820	HPLC-UV	(Zhang et al., 2016)
Bread	14.8 – 17.1	HPLC-DAD	(Gülcan et al., 2020)
Breakfast cereals	15 – 717	HPLC-UV	(Rada-Mendoza et al., 2002)
Brown sugar	0.2 – 6.5	HPLC-DAD	(Polvková & Šimko, 2017)
Coffee	900 – 1200	HPLC-UV	(Alcantara et al., 2021)
Cracker	0.3 – 35.0	HPLC-UV	(Švecová & Mach, 2017)
Corn and cane syrups	407 – 2121 and 461 – 893	HPLC-UV	(Andrade et al., 2016)
Corn syrups	47 – 1655	UV	(Andrade et al., 2017)
Dried fruits	4 – 2400	HPLC-DAD	(Aktağ & Gökmen, 2020)
Dulce de leche	315 – 465	HPLC-DAD	(Barrera et al., 2021)
Fruit juice	0.1 – 3.0	GC–MS/MS	(Marsol-Vall et al., 2016)
Honey	12 – 127	CE and HPLC-MS/MS	(Rizelio et al., 2012)
Honey	2 – 232	NIR	(Apriceno et al., 2018)
Honey	11 – 162	UV/Vis	(Besir et al., 2021)
Milk products	37 – 891	HPLC-DAD	(Xing et al., 2021)
Thermally-processed seafood	0.01 – 2.3	HPLC-MS/MS	(Qin et al., 2017)
Tomato-based products	5 – 312	CE	(Marcondes et al., 2021)
Vinegar	43 – 455	HPLC-UV	(Gong et al., 2020)
Wine	0.2 – 598	HPLC-DAD-MS/MS and NMR	(Serra-Cayuela et al., 2013)

CE = Capillary electrophoresis; DAD = Diode-Array Detection; GC = Gas Chromatography; HPLC = High Performance Liquid Chromatography; MS/MS = Tandem mass spectrometry; NIR = Near Infrared Spectroscopy; NMR = Nuclear magnetic resonance spectroscopy; UV = Ultraviolet spectrophotometry; UV/Vis = Ultraviolet–visible spectrophotometry.

and accumulation of this compound are affected by the system temperature and water activity (Purlis, 2010).

HMF is acceptable in some foods because of its relation to sensory properties (color, flavor, and smell) and quality markers of thermal processing and/or inadequate storage conditions, such as coffee, fermented soy sauce, and bread (Albouchi & Murkovic, 2019; Zhang & Li, 2019). It was demonstrated for milk that moderate heating (e.g. 110–120 °C for 30 min) increased HMF concentration, whereas high temperatures (e.g. 130–140 °C for 25 min or 150 °C for 10 min) promoted its degradation (Morales & Jiménez-Pérez, 1998), demonstrating the feasibility of its use as a marker of the thermal processing.

The HMF formed during coffee roasting due to the Maillard reaction is one of the main components of the aroma of the product (Preedy, 2015). When HMF was determined in specialty and traditional coffees, the concentrations were significant only in the former because of less intense roasting. This species may then be exploited either as a marker of the roasting process or to discriminate between specialty and traditional coffees (Alcantara et al., 2021; Mehaya & Mohammad, 2020).

Food industries use diverse colorants in the formulations of foodstuffs because the color of the final product is an important sensorial factor. The food colorants caramel I, II, III, and IV colors (international numbering systems 150a, 150b, 150c, and 150d, respectively) are widely used for this purpose (Damodaran & Parkin, 2017; Martins, Sentanin, & De Souza, 2020; Msagati, 2012). They are produced by the caramelization of carbohydrates with or without the addition of sulfites and/or ammonia, and HMF is generated depending on the processing conditions (Martins et al., 2019, 2020).

Because of toxicity, the HMF concentration must be regulated in foodstuffs. The *Codex Alimentarius*, European Union (EU), and the United States regulations established the limit of HMF only for honey, which varies from 40 to 80 mg kg^{-1}, depending on the country of origin. Likewise, the International Federation of Fruit Juice Processors recommends a maximum concentration of 10 mg L^{-1} in fruit juice and 25 mg L^{-1} in concentrated fruit juices, whereas the *Codex Alimentarius* establishes that 25 mg kg^{-1} in apple juice indicates deterioration and/or inadequate thermal treatment. Despite its relevance, the maximum quantity of HMF in other foodstuffs has not been established (Capuano & Fogliano, 2011; ECHA, 2021; FAO/WHO, 2019; Lee et al., 2019). HMF concentration can be minimized through changes in some processing steps in industrialized foods, such as ultraviolet irradiation, the addition of phytochemicals, yeast fermentation, vacuum treatment, microwave heating, non-thermal processing, and modification of food composition (Barrera et al., 2021; Lee et al., 2019; Ros-Polski et al., 2016).

The roasting of bread was evaluated under nitrogen, carbon dioxide, or sulfur dioxide streams. The HMF generation decreased significantly with the use of carbon and sulfur dioxides, while it did not differ significantly from that of the control sample with the use of nitrogen (Gülcan et al., 2020). These results reflect the effect of an oxidizing atmosphere in the thermal processing. Some non-thermal processes, such as ultra-high-pressure homogenization and pulsed electric fields, have been employed to increase the shelf life of foodstuffs and to decrease the HMF concentration. Thus, high-sugar syrup was pasteurized with irradiation (Ultraviolet-C at 254 nm), which can be used as an alternative to prevent HMF formation through minimization of the caramelization reaction rate (Ros-Polski et al., 2016).

Because of the HMF volatility, post-process vacuum treatment may be exploited to remove it from foodstuffs, but the applicability is limited by the characteristics and physicochemical properties of the sample. The foodstuffs need to be hydrated before the vacuum process to remove HMF and some sensory properties can change. Hence, the optimization of processing parameters (temperature, time, water content, and pressure) is essential for ensuring the quality of foodstuffs (Anese et al., 2013; Shapla et al., 2018).

4. HMF analysis

A literature survey from the *Web of Science* database demonstrated the importance of the determination of HMF in food, with 204 papers published worldwide from 2001 to 2021 (e.g., Spain, Brazil, Italy, China, Portugal, USA, and Canada). Most publications refer to high-impact factor journals (IF > 2.0), and received 8764 citations, corresponding to a mean of 42.96 citations per article. Fig. 2a presents the main foodstuffs (honey, cereals and their derivatives, beverages, fruits and vegetables, coffee, and infant formula), in which HMF has been determined. These foodstuffs can be adulterated and/or subjected to inadequate thermal processing, yielding abnormal HMF concentrations (Capuano & Fogliano, 2011; Nielsen, 2014).

Various analytical techniques have been used for HMF determination in different foodstuffs and monitoring chemical processes. Fig. 2b shows a bibliographic survey of spectrometric, chromatographic, and electro-analytical techniques. The predominance of chromatographic techniques is due to the inherent selectivity and complexity of food samples (Lundanes, Reubsaet, & Greibrokk, 2014; Vitha, 2016). Notably, there has been an increase in the number of applications involving spectrometry over the last years, owing to practical aspects. Electroanalysis has seldom been employed for HMF determination, but some recent contributions have been presented. An overview of the analytical techniques applied to HMF determination is presented in Table 2.

4.1. Spectrometric methods

Molecular spectroscopy has been useful for determining HMF in foodstuffs by exploiting different principles and electromagnetic radiation ranges (ultraviolet, visible, and infrared) (Pasias et al., 2017;
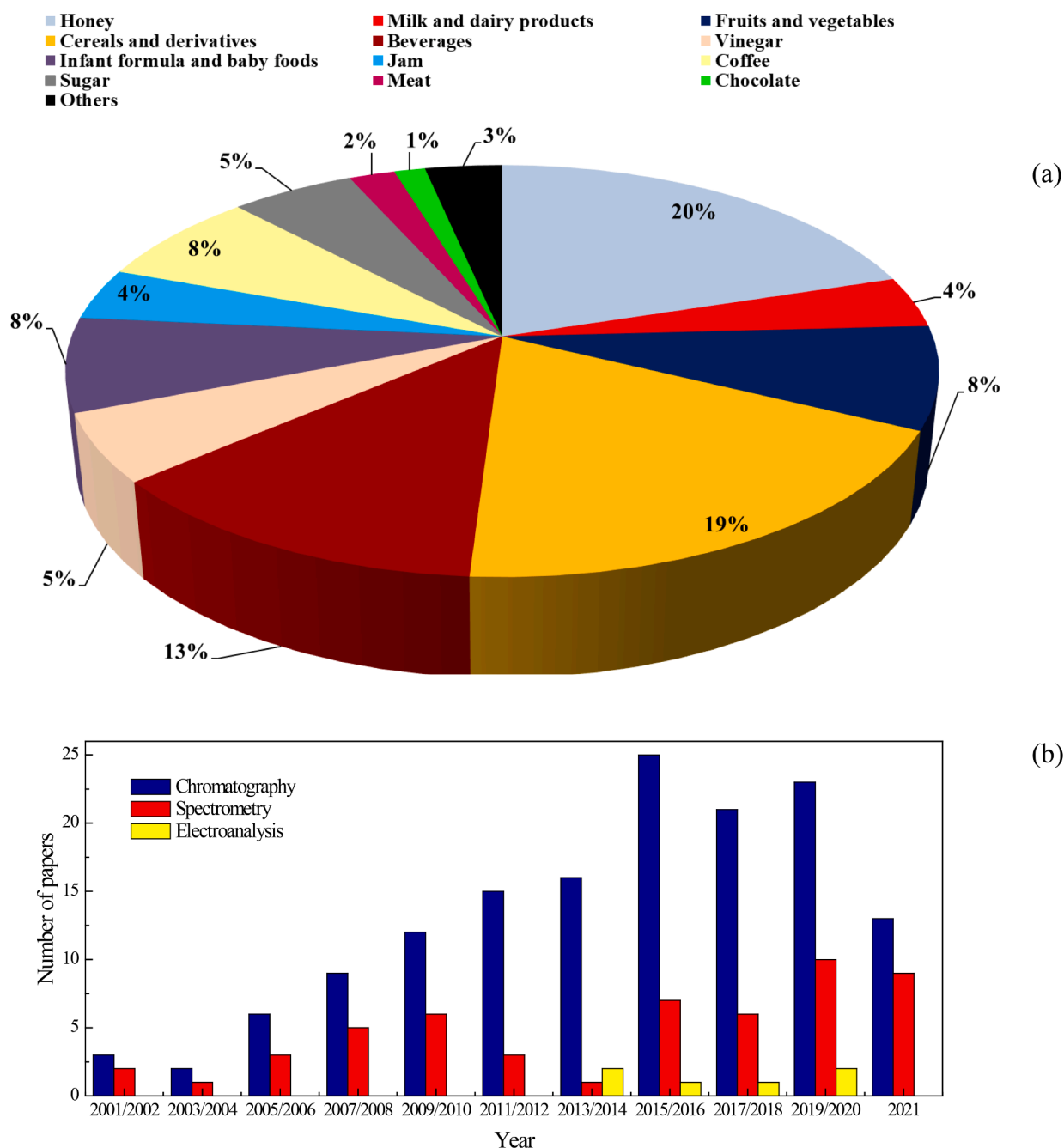

Fig. 2. Distribution of analytical methods for HMF determination relative to (a) the food group analyzed and (b) analytical technique.

Table 2
Comparison of analytical techniques for HMF analysis.

Analytical parameter	Spectrometry					Chromatography			Electroanalysis		
	Raman	NMR	UV/Vis	NIR	MS	HPLC	UHPLC	GC	CV	SWV	Amperometric
Precision (%)	Not reported	Not reported	2.1 – 5.5	Not reported	Not reported	0.6 – 8.0	0.31–10.1	12.0 – 20.0	5.5	1.6	3.7 – 4.7
Recovery (%)	Not reported	92.0 – 98.3	93.5 – 106	Not reported	Not reported	83.0 – 105.0	82.8 –146.4	79.0 – 115.0	90.2 – 104.7	98.4 – 102.9	95.0 – 99.0
Selectivity	Good	Good	Good	Poor	Excellent	Excellent	Excellent	Excellent	Poor	Good	Good
Sensitivity	Good	Good	Good	Poor	Excellent	Good	Good	Good	Poor	Excellent	Good
Robustness	Good	Good	Excellent	Moderate	Excellent	Good	Good	Good	Poor	Good	Poor
Sample throughput	High	Moderate	Moderate	High	High	Low	Moderate	Low	Moderate	High	High
Sample preparation	Not required	Not required	Moderate	Not required	Low	High	High	High	Low	Low	Low
Derivatizatization	No	No	Yes	No	No	Yes	Yes	No	No	No	No
Cost	Moderate	High	Low	Low	High	Moderate	High	Moderate	Low	Low	Low
Applicability to HMF analysis	Low	Low	Moderate	Low	Low	High	Moderate	Moderate	Low	Low	Low

CV = Ciclic voltammetry; GC = Gas chromatography; HPLC = High-performance liquid chromatography; MS = Mass spectrometry; NIR = Near infrared spectroscopy; NMR = Nuclear magnetic resonance spectroscopy; SWV = Square-wave voltammetry; UHPLC = Ultra high performance liquid chromatography; UV/Vis = Ultraviolet–visible spectrophotometry.

Tallarico et al., 2021). It is also the predominant approach for detection by chromatography. The HMF chemical structure has chromophores/fluorophores that enable the exploitation of absorption and/or fluorescence techniques. Moreover, chemical derivatization has been exploited to improve selectivity (Andrade et al., 2017; Baş & Gürkan, 2021; Besir et al., 2021; Christian et al., 2014; Gürkan & Altunay, 2015; Milani et al., 2017; Pasias et al., 2017). Table 3 highlights some applications of molecular spectroscopy for determining HMF in different foods. Some articles were not focused on the development of a method for quantification and/or identification of HMF; instead, they applied the methodologies from the literature for e.g. monitoring formation or consumption of HMF. Hence, information on the analytical features (e. g., precision, detection limits, and recoveries) is lacking in these articles.

UV/Vis spectrophotometry is attractive for HMF determination because of its simplicity, cost-effectiveness, and speed. It also enables sample processing in flow analysis (Cerdà et al., 2018) and agrees with green analytical chemistry (GAC) guidelines. Nonetheless, sample pretreatment and/or analyte derivatization is required to improve selectivity and avoid matrix effects, which is a time-consuming process (Christian, Dasgupta, & Schug, 2014; Nunez & Lucci, 2016). An additional drawback is the relatively high detection limits (LOD) achieved in some applications, e.g., 51 mg L^{-1}, (Pasias et al., 2017), which hinders the application of the method to some samples. The procedure proposed by Baş & Gürkan (2021), based on the formation of the imine adduct and ion-pair with phenosafranine, stands out because of the low LOD achieved (0.8 µg L^{-1}).

The HMF in honey was determined by UV/Vis spectrophotometry after reaction with resorcinol in an acid medium, yielding a red product according to the Seliwanoff test (Besir et al., 2021). The sample treatment involved dissolution in water and the addition of 15% (w/v) potassium hexacyanoferrate(II) and 30% (w/v) zinc acetate. The mixture was centrifuged for 15 min at 5000 rpm at 4 °C, the supernatant was separated, and the resorcinol-HCl reagent was added. The obtained product was measured at 485 nm with good recoveries (ca. 96%) and results agreed with those from reference methods (spectrophotometric Winkler method and high-performance liquid chromatography (HPLC) coupled to UV detection) (Besir et al., 2021).

A spectrophotometric method based on the reaction between phenosafranine and HMF in citrate buffer pH 5.5 with sodium dodecyl sulfate was proposed for determining HMF in food samples. Initially, the pH of the samples (flower and pine honey, grape, carob, pomegranate, jams, cherry berry, and vinegar) was adjusted to 7.0, and samples were processed with or without sonication. After adding Triton X-114 for cloud point extraction, the solution was sonicated at 45 °C for 12 min and centrifuged at 3000 rpm for 10 min to obtain the surfactant-rich phase at the bottom of the tube for preconcentrating HMF. The surfactant-rich phase was diluted in ethanol and measured by UV/Vis spectrophotometry at 532 nm with good precision (RSD, 3.0–4.2%) and accuracy (95–99%), enrichment factor of 37.5, and low LOD (0.5–0.7 µg L^{-1}) (Baş & Gürkan, 2021).

The thermal processing of garlic was evaluated by determining some compounds produced in the Maillard reaction, such as HMF, which was measured by UV–Vis spectrophotometry at 550 nm after chemical derivatization with p-methylaniline and barbituric acid (Li et al., 2020).

Table 3
Applications of spectroscopic techniques for HMF determination in foodstuffs.

Sample	Technique	Conditions	RSD (%)	LOD (µg L^{-1})	Recovery (%)	Reference
Honey	^{1}H NMR	pH adjustment to 4.9 and addition of TSP	—	—	92.0 – 98.3	(He et al., 2020)
Corn syrups	UV (285 nm)	Reduction with sulfite	0.3	100	—	(Andrade et al., 2017)
Honey	UV/Vis (485 nm)	Reaction with Seliwanoff reagent (resorcinol-HCl)	2.5 – 5.1	2690	95.8 – 96.6	(Besir et al., 2021)
Honey	UV (284 and 336 nm)	Treatment with sodium bisulfite	9.7	51000	101.7	(Pasias et al., 2017)
Honey	UV/Vis (532 nm)	Formation of the imine adduct and ion:pair with phenosafranine in SDS medium	3.0 – 4.2	0.5 – 0.7	95.0 – 99.0	(Baş & Gürkan, 2021)
Honey	UV (284 and 336 nm)	Reaction with p-nitrophenylhydrazine in SDS medium	2.1 – 3.6	1960 – 6500	93.5 – 103.2	(Gürkan & Altunay, 2015)
Sugarcane liquor	UV/Vis (420 nm)	Reaction with p-aminobenzoic, barbituric and hydrochloric acids	3.2 – 5.5	740	96.3 – 106.0	(Milani et al., 2017)

[1] H NMR = proton nuclear magnetic resonance; LOD = detection limit; NIR = Near infrared spectroscopy; RSD: relative standard deviation; SDS = sodium dodecyl sulfate; TSP = trisodium phosphate; UV/Vis = ultraviolet –visible spectrophotometry.

Sample pretreatment was similar to that adopted by Besir et al. (2021), involving dilution in water, the addition of potassium ferrocyanide and zinc sulfate, and sonication for 30 min.

Ultrasonic-assisted cloud point extraction was used to preconcentrate the HMF from orange, apple, cherry, peach, mandarin, and lemon juices, as well as beer, wine, tea, soft drinks, and vinegar (Gürkan & Altunay, 2015). Initially, the samples were processed using two methodologies to minimize interference. Thus, perchloric acid, potassium hexacyanoferrate(II), and zinc acetate were added, and the obtained solutions were either heated at 45 °C for 15 min under magnetic stirring or sonication, or at 40 °C for 5 min, followed by centrifugation. The treated samples were filtered, and the pH was adjusted to 7.0. HMF reacted with p-nitrophenylhydrazine and sodium dodecyl sulfate at pH 4.0 to selectively form a product, which was extracted using Triton X-45. The surfactant-rich phase was analyzed by UV/Vis spectrophotometry at 385 nm with good precision (RSD, 2.1–3.6%) and accuracy (recoveries within 97.0–98.8%), and low LOD (1.96 µg L^{-1}) (Gürkan & Altunay, 2015).

Raman spectroscopy has some advantages for food analysis, such as fast measurements and the possibility of direct analysis in liquid and solid foodstuffs, including low susceptibility to the water content in the samples. However, a disadvantage is a low sensitivity for the determination of target compounds (Colthup et al., 1990; Li & Church, 2014). Raman spectroscopy was used to evaluate the composition of honey through the determination of total flavonoids, total phenol, proline, and HMF, as well as evaluation of physicochemical properties (Anjos et al., 2018). The samples were analyzed without any pretreatment by irradiation with a 500 mW laser source with a spectral range of 3500–70 cm^{-1}. Data processing by Fourier transform and spectral decomposition enabled the determination of analytes with analytical features similar to those in the literature. Calibration was performed with partial least squares using several honey samples to minimize the matrix effect, which enabled HMF determination from 0.5 to 17.3 mg kg^{-1} (Anjos et al., 2018).

Mass spectrometry (MS) is characterized by high sensitivity and selectivity, as well as the capability for simultaneous analysis. Its disadvantages include high acquisition and maintenance costs, and the need for highly skilled analysts (Hoffmann & Stroobant, 2008). Electrospray ionization/quadrupole time-of-flight MS was employed to determine the intermediates of the Maillard reaction of glucose with alanine. HMF was detected in a methanol medium as [M + H]$^+$ at m/z 127.0389 ($C_6H_7O_3$) without the interference of divalent iron (Kim & Yaylayan, 2021).

Near infrared spectroscopy (NIR) is widely used in food analysis, with quick analyses, without sample processing or with simple pretreatments, thus avoiding waste generation. The limited sensitivity may hinder HMF determination and the need for multivariate calibration may be a disadvantage for some users (Hoffman, 2005; Babushkin et al., 2016). However, two analytical methods exploited NIR with chemometrics and/or Fourier transform to detect HMF in honey (Apriceno et al., 2018) and monitor the conversion of cellulose into lactic acid (Tallarico et al., 2021), with accuracy assessment with HPLC-UV. The determination of HMF in the range 10–231 mg kg^{-1} was realized from spectra obtained from 4000 to 10,000 cm^{-1}. The measurements were based on the second overtone of CH stretching (8305 cm^{-1}) and the first and second overtones of OH stretching of water at 5154 cm^{-1} and 6812 cm^{-1}, respectively.

Combining proton nuclear magnetic resonance (H^1 NMR) spectroscopy and multivariate calibration quickly detects HMF with good reproducibility (Günther, 2013). In this sense, H^1 NMR was used to evaluate the formation of HMF from the cellulose of banana plant waste by comparing the chemical shifts (Flores-Velázquez et al., 2020). The samples were dissolved in deuterated dimethyl sulfoxide, and the obtained products were dissolved in deuterated water. H^1 NMR and multivariate statistical analyses were also combined for honey authentication by means of target compounds, including HMF (He et al., 2020).

Samples were diluted in deuterated phosphate buffer (pH 4.9) with sodium 3-(trimethylsilyl)-2,2,3,3-^{2}H$_4$ propionate. The mixture was centrifuged for 10 min at 10,000 rpm before analyzing the supernatant.

4.2. Chromatographic methods

Chromatographic techniques have been widely employed to separate, identify, and quantify the HMF in foodstuffs, improving selectivity in the analysis of complex samples. Furthermore, other target compounds can be identified for food authentication and quality control (Nielsen, 2014). Table 4 highlights recent contributions involving gas chromatography (GC) or HPLC.

The most common detectors for HMF determination by GC are MS (Chang et al., 2021; Cui et al., 2020; Marsol-Vall et al., 2016; Vazquez et al., 2021) and flame ionization (Gaspar & Lopes, 2009). Mass spectrometry has been preferred because of its high sensitivity and selectivity in the simultaneous determination and identification of diverse target volatile compounds, and it has been applied for HMF determination in different foodstuffs, including pear and apple juices, honey, and dairy products (Shalliker, 2011). As highlighted in Table 4, helium and polyethylene glycol predominate as the mobile and stationary phases, respectively. The run times vary from 12.2 to 32.2 min, with good precision (RSD < 20%) and acceptable accuracy, the latter typically evaluated as recovery values (79 – 115%). The reported LODs (from 1.6 to 20 µg L^{-1}) are suitable for HMF determination in several food samples.

The HMF and patulin (4-hydroxy-4H-furo[3,2-*c*]pyran-2(6H)-one) in juices and concentrates of apples and pears were determined using GC–MS. Derivatization of the target compounds with N-methyl-N -(trimethylsilyl) trifluoroacetamide at the injection port was carried out at 270 °C, with a 1:2 sample to derivatization reagent ratio, enabling low LOD (1.6 µg kg^{-1}), good precision (RSD, 2.3 – 8.4%), and a run time of 12.2 min. Sample pretreatment involved extraction of the analytes with ethyl acetate due to its compatibility with GC, enabling the determination of HMF in the 0.14 to 3.05 µg/g range (Marsol-Vall et al., 2016).

Two analytical methods exploited GC–MS for determining the HMF in conjunction with other analytes in dairy products (fermented, reconstituted, pasteurized, and UHT milk, milk powder, and yogurt) (Cui et al., 2020) and honey (Vazquez et al., 2021). The HMF was determined with reasonable accuracy (recoveries in the 79–115% range) and precision (RSD, 12–20%), low LODs (0.002 – 0.02 mg kg^{-1}), and relatively short run times (17.2 and 32.0 min). Modified QuEChERS was employed to extract furfurals: the sample/acetonitrile mixture was vortexed, sonicated, and centrifuged (6000 rpm for 5 min), before the addition of anhydrous magnesium sulfate, primary secondary amine, and C18 to the supernatant, followed by vortexing and centrifugation (5000 rpm for 5 min). The organic phase was filtered and analyzed by GC–MS/MS (Cui et al., 2020) or GC-MS (Vazquez et al., 2021).

Celestolide and 1-octanol were used as internal standards to determine the HMF and other analytes (e.g., furfural and phenylfurane) in honey by GC–MS after solid-phase microextraction. Samples in acetone/ water medium were magnetically stirred at 100 °C until equilibrium was achieved with the divinylbenzene/carboxen/polydimethylsiloxane fiber in the headspace (30 min) for extraction of the target compounds. The analytes were immediately desorbed in the GC injection port for 5 min at 270 °C for chromatographic analysis (Vazquez et al., 2021).

Under suitable conditions, HPLC enable the simultaneous determination of HMF in foodstuff samples with excellent resolution, adequate recoveries (83–106%), and high precision (RSD, 0.6–8.0%), as shown in Table 4. However, the run times and LODs varied significantly, from 2.5 to 90.0 min and 0.10 – 150 µg kg^{-1}, respectively. The most commonly used HPLC detectors for HMF determination are UV spectrophotometry (Alcantara et al., 2021; Gong et al., 2020; Nguyen et al., 2016; Sabater et al., 2018), MS (González, Morante-Zarcero, Pérez-Quintanilla, & Sierra, 2020; Qin et al., 2017), amperometry (Xu et al., 2015), and fluorescence (Sun et al., 2017). The UV spectrophotometry and MS detectors

Table 4
Applications of chromatographic techniques for the determination of HMF in foodstuffs.

Sample	Technique	Column / mobile phase	Run time (min)	RSD (%)	LOD (μg L^{-1})	Recovery (%)	Reference
Honey	GC–MS	50 m × 0.20 mm, 0.20 μm[a] / helium	32.0	12.0 – 20.0	—	—	(Vazquez et al., 2021)
Apple and pear juice	GC–MS/MS	30 m × 0.25 mm, 0.25 μm[b] / helium	12.2	2.3 – 8.4	1.6	—	(Marsol-Vall et al., 2016)
Dairy products	GC–MS/MS	30 m × 0.25 mm, 0.25 μm[a] / helium	17.2	13.1	20.0	79.0 – 115.0	(Cui et al., 2020)
Dairy products	HPLC-DAD (284 nm)	150 mm × 4.6 mm, 5 μm[c] / acetonitrile and water (isocratic)	10.0	2.0 – 4.1	19.5	89.0 – 91.9	(Barrera et al., 2021)
Breakfast food	HPLC-DAD (280 nm)	150 mm × 4.6 mm, 5 μm[c] / acetonitrile and 0.2 mol L^{-1} phosphoric acid (gradient)	160	—	—	—	(Ghazouani et al., 2021)
Vegetables, meat-based, and fruit-based baby foods	HPLC-DAD (284 nm)	100 mm × 4.6 mm, 3.5 μm[c] / acetonitrile and water (gradient)	14.0	1.0 – 6.0	150.0	83.0 – 105.0	(Prata et al., 2021)
Honey	HPLC-FLD (320 and 390 nm)	250 mm × 4.6 mm, 5 μm[c] / acetonitrile and water (gradient)	90.0	3.9 – 5.7	0.01	96.9 – 103.6	(Zhang et al., 2018)
Bovine milk powder	HPLC-FLD (322 and 447 nm)	150 mm × 4.6 mm, 5 μm[c] / acetonitrile and water (gradient)	30.0	0.7 – 5.1	0.1	96.7 – 98.8	(Sun et al., 2017)
Carbonated drink and soft drink	HPLC-MS/MS	50 mm × 2 mm, 2.5 μm[c] / methanol and water (gradient)	5.0	2.3 – 3.5	0.1	85.1 – 101.0	(Feng et al., 2017)
Thermally-processed seafood products	HPLC-MS/MS	50 mm × 2 mm, 2.5 μm[c] / methanol, formic acid and water (isocratic)	2.3	2.3 – 3.5	0.8	87.0 – 102.0	(Qin et al., 2017)
Cereal, breakfast, and insect bars	HPLC-MS/MS	150 mm × 2.0 mm, 3.5 μm[c] / methanol, water with 0.1% formic acid and 2 mmol L^{-1} ammonium acetate (gradient)	17.0	1.7 – 8.0	11.0	99.0 – 102.0	(González et al., 2020)
Prebiotic-supplemented infant formula	HPLC-UV (283 nm)	250 mm × 4.6 mm, 5 μm[c] / methanol and water (isocratic)	23.0	—	0.3	—	(Sabater et al., 2018)
Coffee	HPLC-UV (280 nm)	250 mm × 4.6 mm, 5 μm[c] / acetonitrile and acetic acid in water (gradient)	30.0	—	100.0	—	(Alcantara et al., 2021)
Biscuits	HPLC-UV (284 nm)	150 mm × 4.6 mm, 5 μm[c] / acetonitrile and water (gradient)	20.0	—	1000	—	(Nguyen et al., 2016)
Chinese traditional fermented vinegar	HPLC-UV (284 nm)	250 mm × 4.6 mm, 5 μm[c] / 10% methanol and water (isocratic)	—	—	145.0	91.6 – 106.3	(Gong et al., 2020)
Corn and sugarcane syrups	HPLC-UV (285 nm)	150 mm × 4.6 mm, 5 μm[c] / acetonitrile and 0.5% formic acid (isocratic)	8.0	0.6 – 6.4	90.0	100.0 – 104.0	(Andrade et al., 2016)
Fructus Corni	UHPLC-UV (240 nm)	100 mm × 2.1 mm, 1.7 μm[c] / methanol and acetic acid in water (gradient)	12.5	2.6 – 4.7	20.0 – 80.0	95.2 – 103.0	(Du et al., 2018)
Coffee	UHPLC-UV (280 nm)	50 mm × 2.1 mm, 1.7 μm[c] / methanol and 0.2% formic acid (gradient)	13.0	1.9 – 8.5	0.7	105.0 – 108	(Macheiner et al., 2021)
Meatballs	UHPLC-MS/MS	100 mm × 2.1 mm, 1.7 μm[c] / methanol and 0.1% formic acid (gradient)	4.5	0.31 – 6.6	0.6	82.8 –119.9	(Sun et al., 2022)
Seafood	UHPLC-MS/MS	100 mm × 2.1 mm, 1.8 μm[c] / acetonitrile with 0.1% formic acid (gradient)	20.0	7.1 – 10.1	20.0	85.0 – 99.8	(Qin et al., 2021)

CE = capillary electrophoresis; DAD = diode array detection; FLD = fluorescence detection; GC = gas chromatography; HPLC = high-performance liquid chromatography; LOD = detection limit; MS = mass spectrometry; MS/MS = tandem mass spectrometry; RSD: relative standard deviation; UHPLC = ultra-high performance liquid chromatography, UV = ultraviolet spectrophotometry.

[a] polyethylene glycol.

[b] 5%-phenyl-methylpolysiloxane.

[c] C18.

are predominant owing to their cost-effectiveness and sensitivity, respectively.

Two analytical methods employed HPLC with diode array detection to determine the HMF in baby foods (Prata et al., 2021) and *dulce de leche* (Barrera et al., 2021). In the former, analytes were extracted from the samples with acetonitrile and hexane under vortex and centrifugation. The bottom phase was re-extracted under the same conditions, the supernatants were combined and diluted in deionized water and filtered before analysis. The procedure yielded good recoveries (83–105%) and precision (RSD = 1.0–6.0%), LOD of 150 μg kg^{-1} and run time of 14 min (Prata et al., 2021). Another procedure exploited the heating of samples with oxalic acid for 25 min at 100 °C, before the addition of trichloroacetic acid for protein precipitation. The mixture was stirred and centrifuged for 15 min at 4000 rpm, the procedure was repeated, and the supernatants were filtered and diluted in water before chromatographic separation. Good recoveries (89–92%) and precision (RSD, 2.0–4.1%), as well as low LOD (19 μg kg^{-1}) were achieved with run times within 10 min (Barrera et al., 2021).

The HPLC with fluorescence detection was exploited to determine HMF and furfural in honey and coffee, achieving good accuracy (96.9–103.6 %) and precision (RSD, 3.9–5.7%) with simple sample pretreatments, restricted to sample dissolution. The analytes were derivatized with 4-hydroxylaminopropyl-7-methoxylcoumarin, which significantly improved the sensitivity. Furthermore, the methodology prevented the formation of HMF from the sample during the analytical routine, yielding results in agreement with GC–MS (Zhang et al., 2018).

The potential of ultra-high-performance liquid chromatography (UHPLC) to decrease the volume of the solvents and improve the resolution of chromatographic separations has also been exploited for HMF determination in food (Naushad & Khan, 2014; Xu, 2017). Furfurals, including HMF, were determined in coffee by UHPLC-UV after extraction with 2-furoic acid. Subsequently, 15% w/v sodium hexacyanoferrate(II) and 30% w/v zinc sulfate heptahydrate were added to the extract. The supernatant was extracted twice with 2-furoic acid. All

extracts were combined and diluted in phosphate buffer (pH 8.0), centrifuged, and filtered. This methodology allowed for the determination of the HMF within 5.0 min with good analytical performance, such as good precision (RSD, 1.9–8.5%) and recovery (105–108%), and low LOD (0.7 µg L^{-1}) (Macheiner et al., 2021).

4.3. Electroanalytical methods

HMF is an electroactive species, and this property has been exploited to develop electroanalytical methods for its determination in foodstuffs. The bibliographical survey from 2001 to 2021 showed a predominance of voltammetry (cyclic voltammetry, CV, and square wave voltammetry, SWV) in the determination of HMF, with the predominance of applications focused on fruit juices, honey, and soft drinks.

Cyclic voltammetry allows the evaluation of adsorption processes, chemical and electrochemical reaction kinetics, the reversibility of redox reactions, and reaction mechanisms (Salhi et al., 2020; Scholz, 2010). The SWV has been employed for HMF determination owing to its higher sensitivity and selectivity than other voltammetric techniques. In addition, this technique has been used to evaluate electrochemical mechanisms involving HMF in foodstuffs (Mirceski et al., 2007; Scholz, 2010; Wang, 2006).

Recent studies have employed metal- or carbon-based electrodes to determine HMF, which have low toxicity compared with the mercury-based electrode and provide reactions in the anodic potential interval. The carbon-based electrodes are the most common, which yield good analytical features (e.g., precision and LOD) and make an environmentally friendly analytical determination feasible. Moreover, they are characterized by low background current, cost-effectiveness, chemical inertia, and good mechanical stability. These electrodes can be made from different forms of carbon, such as carbon paste, glassy carbon, boron-doped diamond, and carbon fiber, thus requiring specific cleanliness and pretreatment procedures (Barsan et al., 2015; Wang, 2006; Zoski, 2007).

Simultaneous determination of HMF and patulin at a glassy carbon electrode coupled with SWV and CV in acetonitrile with tetrabutylammonium perchlorate medium achieved a recovery of 84% (Chanique et al., 2013). This methodology enabled the determination of analytes at concentrations below the maximum limits established by international legislation in apple juice.

The glassy carbon electrode in Na$_2$SO$_4$ solution was used for HMF determination by CV and SWV, yielding a single irreversible cathodic peak at −1.6 V, vs. SCE involving the transfer of two electrons. The reaction was controlled by diffusion, with a diffusion coefficient of 2.23 × 10^{-6} cm^2 s^{-1}, as calculated from the cyclic voltammogram. Analytical curves employing the CV and SWV covered the linear ranges 0.15–1.26 mg L^{-1} and 0.03–0.38 mg L^{-1}, respectively, and the HMF determination in honey was accurate (98–103%) and precise (RSD, 1.2–2.2%) (Salhi et al., 2020).

Simultaneous determination of HMF, 2-methylimidazole, and 4-methylimidazole in soft drinks was performed by amperometry using an amino trap column coupled with a gold working electrode. The samples were degassed by magnetic stirring for 30 min after acidification. The analytes were extracted in a cation-exchange cartridge and eluted using methanol and ammonia (5% v/v). Posteriorly, the extract was evaporated and dissolved in deionized water for electrochemical determination, achieving low LOD (0.3 mg L^{-1} HMF), excellent accuracy (recovery within 95–99%), and good precision (RSD within 3.7–4.7%), thus enabling the determination of the target compounds in food samples (Xu et al., 2015).

5. Conclusions and perspectives

This review discussed the role of HMF in foodstuffs, including its formation, relevance, strategies for controlling its generation in food processing, and recent analytical methods for its determination. HMF forms by industrial processing, storage, and transportation of foodstuffs through the Maillard reaction and caramelization. Hence, its concentration indicates the process efficiency or non-conformities (juice, coffee, cereals, and dairy products), adulteration and traceability (e.g. honey).

The process optimization in food industries can control or even prevent the formation of HMF by adjusting the temperature, pressure, composition, pH value, and water activity of the foodstuffs. Approaches to avoid or control HMF generation include ultraviolet irradiation, the addition of phytochemicals, yeast fermentation, vacuum treatment, microwave heating, non-thermal processing, and modification of foodstuff composition.

In relation to the analytical methods, spectrometric techniques stand out owing to the high sampling rate, simple sample preparation, and capability for direct analysis (NMR or Raman). On the other hand, some spectrometric techniques show low selectivity, which is incompatible with some sample matrices. The UV/Vis spectrophotometry is exploited in many applications, especially after chemical derivatization. Spectrometric techniques have potential to be further explored to determine HMF, mainly fluorescence and digital image colorimetry, as well as direct analysis in other samples (e.g. Raman spectroscopy).

Chromatographic techniques have been extensively used because of their high selectivity and the conjunct determination of other compounds, but tipically involve time-consuming sample preparation. HPLC still has considerable potential to be explored, including materials for the stationary phase, strategies for reducing the toxicity and amount of mobile phase, and minimizing the run times in HMF determination. Improvements in GC methods should be focused on the mode of derivatization and sensitivity improvement.

Electroanalytical techniques have rarely been employed for HMF determination. Because they typically exhibit high sensitivity, low cost, and high sample throughput, electroanalytical techniques should be further explored, including the investigation of new working electrode materials, such as modified carbon-based, metal-based, and screen-printed electrodes. Furthermore, studies using these techniques coupled with chromatography and/or flow injection analysis can also be conducted to improve the analytical performance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosure statement

This article does not contain any studies with human or animal subjects. No potential conflict of interest was reported by the authors.

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