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Review

Quantitative strategies for detecting different levels of ethyl carbamate (EC) in various fermented food matrices: An overview

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ABSTRACT

As a potential carcinogen to humans, ethyl carbamate (EC, urethane) can be formed during the production and storage stages of certain fermented foods, and therefore its thresholds for largely consumed alcoholic beverages in several countries have been successively established. Regarding EC analysis, however, its precise and rapid determination is challenged by complex matrix components, low levels of the analyte and simple molecular structure (89.1 Da) without chromophore, thus hindering the production process monitoring and quality control. As a result, although the quantification of EC contents in diverse fermented foods and beverages has been reported for decades, the researches focusing on the development, improvement and optimization of analytical methods are currently still updated in order to overcome the above-mentioned challenges. This review presents an overview of traditional and newly-developed promising tools for trace analysis of EC, and main analytical characteristics were summarized with special emphasis on their intrinsic strengths and weaknesses. In addition, sample preparation strategies commonly used for reducing matrix effects are also described and discussed. The present article contributes to providing better understanding on how to ascertain and improve EC detection techniques matched with suitable sample pretreatment procedures based on the sample characteristics and research purposes.

Contents

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1. Introduction

Fermented foods, including various alcoholic beverages (eg, beer, wine and spirits), are favored by hundreds of millions of people worldwide. The popularity of fermented foods is partially driven by the fact that bioactive components produced and made bioavailable via fermentation process exhibit diverse health-promoting effects (eg., antidiabetic, antiinflammatory, anticholinesterase, antioxidant and blood-pressure-lowering, etc.), thus contributing to the prevention and control of chronic diseases including obesity, type 2 diabetes, cardiovascular disease, and cancer (Martins et al., 2011; Wilburn & Ryan, 2017). However, one concern about the manufacturing and consumption of fermented foods is the balanced health benefits against the risks posed by production process derived hazardous compounds, such as ethyl carbamate (EC) (Hasnip et al., 2007; Li, Zhong, Wang, & Gao, 2017; Wu, Pan, Wang, Shen, & Yang, 2012; Zhang, Si, et al., 2017), biogenic amines (Alvarez & Moreno-Arribas, 2014; Ordóñez, Troncoso, García-Parrilla, & Callejón, 2016), formaldehyde (Shin & Lim, 2012), furfural (Harada et al., 2017) and aflatoxins (Shukla, Kim, Chung, & Kim, 2017; Shukla, Park, Lee, Kim, & Kim, 2014), among others. Particularly, EC has attracted considerable attention due to the progressive understanding on its wide occurrence and potential toxicity to humans, as evidenced by the increasing literature publication in recent years (Fig. 1).

EC is an ethyl ester of carbamic acid and has been recognized as a multi-site carcinogenic compound, causing the incidence of cancer in lung, blood vessels and liver based on animal experiments (Lachenmeier et al., 2010; Narayan & Kumar, 2012). Genotoxic and carcinogenic effects have been confirmed in many species including rats, mice, hamsters and monkeys (Salmon & Zeise, 1991; Vázquez, Prados, Reglero, & Torres, 2017). A two-year study in rodents by National Toxicology Program (NTP) revealed the probable carcinogenicity of EC to humans (Vázquez et al., 2017). Correspondingly, the World Health Organization's International Agency for Research on Cancer (IARC) classified EC into a group 2B carcinogen (possible carcinogenic to humans) in 1974, and then upgraded into group 2A (probably carcinogenic to humans) recently (IARC, 2010). After the

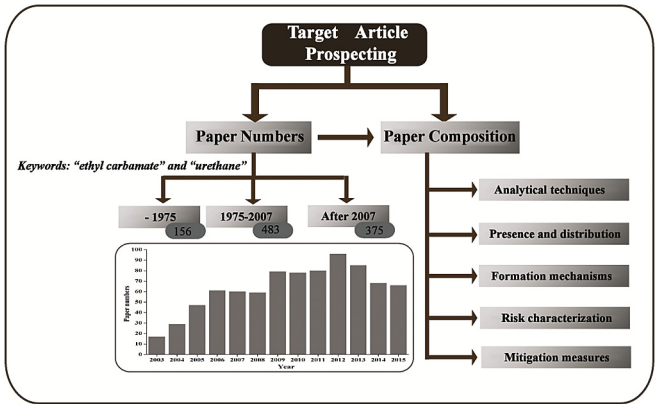

Fig. 1. Graphical representation of article composition concerning ethyl carbamate research based on Google Scholar database.

presence of EC in fermented foods and beverages was firstly reported by Ough (1976), the subsequent analysis in a much wider range of sample matrix types revealed the ubiquitous occurrence and differentiated content distribution of the target compound in various fermented foods and alcoholic beverages (Table 1). For the prevention and reduction of EC contamination, respective criteria have been previously established for those beverages with large consumption in their own countries (Weber & Sharypov, 2009), such as France (distilled spirits/150 μg/L; fruit brandies/1000 μg/L), Germany (fruit brandies/800 μg/L), Swiss (fruit brandies/1000 μg/L) and Czech (wines/30 μg/L; fortified wines/100 μg/L). However, lately, due to a special health concern for EU countries, the EC levels in spirits made from stone fruit and stone fruit marc are required to achieve a target value of 1 mg/L by the European Commission (EC, 2016). Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated Benchmark Dose Lower Limit (BMDL) of EC as 0.3 mg/kg bw per day and the average daily dietary intake (ADI) as 15 ng/kg bw per day (FAO/WHO, 2005; Li et al., 2017). Lately, exposure assessment and risk characterization were conducted in China and Korea, according to their respective characteristics of food items (Chen et al., 2017; Lee, Park, Yoon, Kang, & Kim, 2016).

Previous investigations have stated that EC are mainly formed under non-enzymatic conditions through the reaction of ethanol with nitrogen-containing compounds, including urea (Wu et al., 2014a; Xia, Niu, Wu, & Zhou, 2016; Yang, Kang, Zhou, Chen, & Du, 2015; Zhao, Zou, et al., 2013), carbamyl phosphate (Ough, Crowell, & Gutlove, 1988) and citrulline (Azevedo, Couto, & Hogg, 2002; Liu, Pritchard, Hardman, & Pilone, 1994) as well as cyanide (Ding, Huang, Wu, & Zhou, 2017; Mackenzie, Clyne, & MacDonald, 1990), as summarized in Fig. 2. However, the major pathway for EC production often varies depending on the matrix types, and many influencing factors, such as yeast metabolism (Schehl, Senn, Lachenmeier, Rodicio, & Heinisch, 2007), ornithine (Fang, Dong, Xu, He, & Chen, 2013), arginine (Zhang, Fang, Chen, & Du, 2014), pH (Arena & Manca, 2005), temperature (Wu, Chen, et al., 2012; Xia et al., 2016), copper ions (Aresta, Boscolo, & Franco, 2001), antioxidants (Zhou, Fang, & Chen, 2017) and even lignin (Hashiguchi, Izu, & Sudo, 2012), exert an effect on the formation of EC in fermented foods. Consequently, it is essential to identify the major formation pathway and precursor substances when establishing an efficient mitigation strategy for the specified fermented foods (Bortoletto, Silvello, & Alcarde, 2015; Choi & Koh, 2016; Hasnip, Caputi, Crews, & Brereton, 2004; Zhang, Fang, et al., 2014). On the other hand, EC contamination may primarily originate from storage process (Wu et al., 2014b; Xia et al., 2016), thus making EC inspection necessary across the whole food chain from the processing and packaging stage to the end-stage shelf life. On the basis of this fact, a scientific opinion released by the European Food Safety Authority (EFSA) has noted that the sampling time during EC analysis should be well controlled, as well as no exposure to heat and light in the process (EFSA, 2007).

The establishment of accurate and sensitive detection techniques can be the foundation of EC researches (production process monitoring, microbial metabolism and toxicological aspects). Nevertheless, fermented foods and alcoholic beverages are constituted by a high-complexity sample matrix where numerous interfering compounds co-exist (Ordóñez et al., 2016; Zhang, Lu, Tian, &