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Journal of Chromatography A, 881 (2000) 471–481

JOURNAL OF CHROMATOGRAPHY A

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Review

Analysis of resveratrol in wine by capillary electrophoresis ☆

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Abstract

Capillary electrophoresis (CE) is a new analytical technique that has recently been reported as a method for analysis of resveratrol in wine. Several different separation approaches have been taken in these reports. In comparison with high-performance liquid chromatography (HPLC), CE methods have similar sensitivity and can discriminate between *trans*- and *cis*-isomers of resveratrol. CE methods also show promise for analysis of other flavonoid antioxidants (glycosides and aglycones) in wine.

Keywords: Wine; Food analysis; Reviews; Resveratrol; Antioxidants

Contents

1. Introduction

Resveratrol (3,4,5-*N*-trihydroxystilbene) is an antioxidant that exists as both *trans* and *cis* isomers. It also exists in the glycoside form, which is known as piceid. Resveratrol and piceid are found in many plant materials and are believed to function as a part of the stress (i.e. fungal infection) response of the organism. Resveratrol has been reported to have moderate antifungal activity [1]. In foods, major sources of resveratrol are found in grapes, grape juice, wine, and peanuts [2–4]. Both resveratrol and piceid can be found in grape products with the

☆Published as paper number 12883, Journal Series, Nebraska Agricultural Research Division, Lincoln, NE 68583-0704, USA.

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0021-9673/00/$ – see front matter
PII: S0021-9673(00)00211-9

concentration of the glycoside usually being significantly higher than the aglycone [5]. The relative distribution between the glycosylated and aglycone forms in wines is dependent on a number of factors influenced by fermentation and ecological techniques used [6]. Resveratrol in all its forms, is found in much higher concentration in red grape varieties compared with white grape varieties.

Resveratrol has become a compound of considerable interest because of its suggested health promoting roles. Resveratrol is a factor associated with lowering the risk of coronary heart disease (CHD) [7,8]. CHD has been linked with high intake of saturated fat in the diet, however, an exception to this correlation seems to exist in France [9]. It is thought that the consumption of red wines (i.e. resveratrol) might provide protection against CHD in the French population where a lower incidence of CHD is found. Specifically, resveratrol's positive effect on CHD may be a result of protection against oxidation of LDL [10]. Additional protection against CHD may be gained by resveratrol's ability to inhibit platelet aggregation [11]. Resveratrol has also been suggested as an anticarcinogen. Its chemopreventive properties include the ability to inhibit protein tyrosine kinase activity [12], and inhibition of cytochrome P450 1A1 [13]. It has been reported to slow tumor growth by inhibiting prostaglandin syntheses [14].

The health significance of resveratrol has spawned numerous methods for its measurement in foods. This is especially true for wine where resveratrol was initially identified by Siemann and Creasy [3]. The method of gas chromatography (GC) has been employed by several investigators for resveratrol analysis [3,15–18]. Most GC methods involve derivatization of resveratrol with bis(trimethylsilyl)trifluoroacetamide to enhance volatility [15,16]. The GC approach can resolve both resveratrol isomers with detection limits in the low μM range. However, the extraction and derivatization procedures require a significant amount of time and may result in some *trans* to *cis* isomerization [6].

High-performance liquid chromatography (HPLC) is presently the method of choice for quantitating resveratrol based upon the number of reported applications [6,20–25]. Initial reports using HPLC employed multi step extractions prior to separation, and measured only the *trans* form of resveratrol [3,19]. The sensitivity of detection in HPLC was enhanced significantly using fluorimetric [23] or electrochemical detection [22]. More recently, improved HPLC methods for detection and quantification of *cis*- and *trans*-resveratrol and piceid have been reported [6,19,20]. However, there may be some cause for concern as a problem of inter-method variability has been noted with these methods. Soleas et al. [26] reported a 10-fold difference in resveratrol concentration for the same generic wines. An HPLC method has also been developed to determine the level of *trans*-resveratrol in plasma [27], providing a much needed means to assess the relationship between oral dose and blood levels.

Capillary electrophoresis (CE) is a relatively new separation technique and represents an alternative method for the analysis of a variety of compounds, including antioxidants in food matrices [28,29]. A brief summary of applications using CE for the analysis of antioxidant compounds is shown in Table 1. CE has unique advantages that make it an excellent candidate for analysis of these compounds including, a very small sample size requirement, high efficiency of separation and speed [30–34].

The principle of separation in capillary electrophoresis is based on the differential migration of analytes in an electric field resulting from intrinsic differences in mass to charge ratios. The high field strength typically employed (300 V/cm) results in high efficiency separation. Electroosmotic flow of water from anode to cathode results from the high field strength. This flow creates a pumping action originating at the capillary wall, that is devoid of a radial pressure gradient.

CE separations can also be performed in the micellar mode. Micellar separations utilize surfactants like sodium dodecyl sulfate (SDS) at concentrations above their critical micellar level. SDS micelles are organized into spheres with their nonpolar tails toward the interior and the strongly charged sulfate groups on the surface. In the presence of an electric field, the negatively charged micelles migrate toward the anode. However, the electroosmotic flow of water is substantially greater, and all components are moved to the cathode [35]. Micelles are an

Table 1
Summary of capillary electrophoresis methods for separation of flavonoid antioxidants

Analyte	Separation conditions	Remarks	Ref.
Anthocyanins	160 m*M* sodium phosphate pH 2.1, 0.25 m*M* CTAB	MEKC separation of the flavylium cation form of glycosides (standards in solution)	[47]
Catechin	30 m*M* sodium phosphate buffers of pH 7.00 and 8.85	Multi-component CZE separation of antioxidants in Olive tree leaves at pH 7.00 and separation of red wine at pH 8.85	[46]
	0.1 *M* sodium borate pH 9.5	Multi-component CZE separation in wine (SPE used)	[40]
Epicatechin	30 m*M* phosphate buffers of pH 7.00 and 8.85	Multi-component CZE separation of antioxidants in red wine using direct injection	[46]
	0.1 *M* sodium borate pH 9.5	Multi-component CZE separation in wine (SPE used)	[40]
	0.1 *M* sodium borate pH 9.5	Multi-component CZE separation of antioxidants in red wine following liquid–liquid extraction	[44]
Caffeic acid	30 m*M* phosphate buffers of pH 7.00 and 8.85	Multi-component CZE separation of antioxidants in red wine using direct injection	[46]
	0.1 *M* sodium borate pH 9.5	Multi-component CZE separation of antioxidants in red wine following liquid–liquid extraction	[43]
Kaempferol	25 m*M* sodium borate pH 9.5 with 20% methanol	CZE separation of 33 purified flavonoids (aglycone and glycosides of kaempferol and quercetin)	[48]
Myricetin	30 m*M* phosphate buffers of pH 7.00 and 8.85	Multi-component CZE separation of antioxidants in red wine using direct injection	[46]
Quercetin	200 m*M* sodium borate pH 8.0 50 m*M* SDS, 10% methanol	MEKC separation of 13 flavonoids quercetin, myricetin and kaempherol) extracted from honey	[49]
	30 m*M* phosphate buffers of pH 7.00 and 8.85	Multi-component CZE separation of antioxidants in red wine using direct injection	[46]
	10 m*M* sodium phosphate, 6.0 m*M* sodium borate pH 9.3, 50 m*M* sodium deoxycholate	MEKC (deoxycholate) separation using direct injection. Found much less quercetin,catechin gallic acid, than resveratrol	[38]
Resveratrol	10 m*M* sodium phosphate, 6.0 m*M* sodium borate pH 9.3, 50 m*M* sodium deoxycholate	MEKC multi-component separation *cis*- and *trans*-resveratrol in wine using direct injection	[38]
	25 m*M* sodium borate, 25 m*M* sodium phosphate pH 9.0 75 m*M* SDS	MEKC separation of *trans*-resveratrol in wine using direct injection	[37]
	0.1 *M* sodium borate pH 9.5	Multi-component CZE separation of SPE samples, found only *trans*-resveratrol in wine	[40]
	40 m*M* sodium borate pH 9.5	CZE separation of *cis*- and *trans*-resveratrol in wine after SPE	[41]
	30 m*M* sodium borate, 30 m*M* sodium phosphate, pH 9.2, 15% acetonitrile	MEKC separation of *cis*- and *trans*-resveratrol in wine after SPE	[42]

important part of the separation because analytes can partition between the micelle and the mobile phase buffer, which contributes additional selectivity to the separation. Micelles in this type of separation are referred to as a pseudo-stationary phase. The name often used for this mode of separation is micellar electrokinetic chromatography (MEKC) [35,36].

2. CE analysis of resveratrol

Several reports use CE for the analysis of flavonoid compounds, however, only a few were specifically focused on resveratrol (Table 1). In summarizing these articles, two major differences can be observed in the analytical approach used. Specifical-

ly, the differences concern sample preparation (direct injection or SPE) and mode of separation, capillary zone electrophoresis (CZE) or MEKC.

2.1. CE analysis of resveratrol using direct injection

Two reports used the direct analysis approach for determining resveratrol level in wines [37,38]. Direct analysis has advantages in requiring less time to prepare samples and less opportunity for *trans* to *cis* isomerization. These reports both employed MEKC as the mode of separation. In the work from our laboratory, Chu et al. [37], used SDS as the micellar agent and achieved resolution of *cis*- and *trans*-resveratrol standards in solution. The separation was complete in approximately 15 min and detection for *trans*-resveratrol in wine was limited at about 1–2 μ*M* (Fig. 1). However, when using this protocol on wine samples, the *cis* form co-migrated with another unidentified component and was not quantitated.

The other reported direct injection technique for the CE analysis of resveratrol in wine used deoxycholate as the micellar agent and resolved several antioxidant compounds including: *cis*- and *trans*-resveratrol, quercetin, gallic acid, and catechin [38]. In wine samples these investigators found much higher levels of *trans*-resveratrol than the other antioxidants. This is unusual in that most other reports have found the opposite result, i.e. higher levels of catechin, epicatechin and quercetin than resveratrol [39,40]. No limit of detection was reported for this method.

2.2. CE analysis of resveratrol using solid-phase extraction (SPE)

The solid-phase extraction (SPE) approach prior to CE analysis was used by several investigators [40–42] and resulted in cleaner and more concentrated samples. In addition to concentration, the procedure facilitated identification of antioxidants by altering sample conditions and removing interfering materials. In general, the limit of detection for

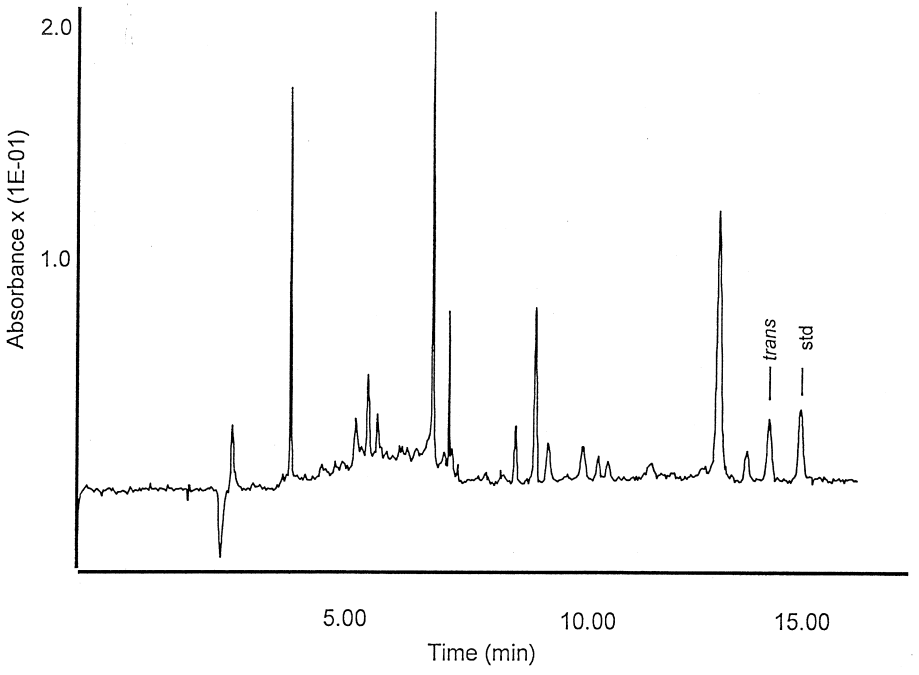

Fig. 1. Electrophoretic separation of red wine after direct injection. Electrophoretic separation of a red wine (California Cabernet Sauvignon). The capillary was fused-silica (50 μm I.D., 30 cm total length) and the separation performed in 75 m*M* SDS, 25 m*M* sodium borate, 25 m*M* sodium phosphate, pH 9.0 at 20 kV. Detection was at 310 nm. The position of *trans*-resveratrol and internal standard 2-[(2-aminoethyl)amino]-5-nitropyridine hydrochloride (std) are indicated. Reprinted with permission from reference [37].

resveratrol determination in wine was lowered 10-fold with good recoveries (95–102%) using SPE [37]. However, major differences in the effectiveness of the SPE procedure could be seen depending on the mode of separation subsequently employed.

2.3. Capillary zone electrophoresis separations

The capillary zone electrophoresis (CZE) method has been shown to separate various types of phenolic compounds [43–47]. Specifically, Kulomaa et al. [46] employed CZE to separate polyphenolic standards in solution and spiked wine. Epicatechin, catechin, quercetin, myricetin and rutin were resolved in red wine. Similarly, Acre et al. [40] identified epicatechin, catechin, quercetin, gentistic acid, caffeic acid, gallic acid and *trans*-resveratrol in separations of spiked wine. The electropherogram of spiked wine sample in this report, also contained a large proportion of unresolved components. This background may have contributed to the reported difficulty in determining the level of resveratrol in wine. Arce et al. [40] found *trans* (but not *cis*)-resveratrol in wines with a 0.36 mg/l (1.5 μM) limit of detection.

Nevado et al. [41] have also used CZE separation of SPE samples to identify both *cis*- and *trans*-resveratrol in wine. The analysis time for this procedure was short (6 min) and the limit of detection was 0.25 mg/l (1.06 μM). Electropherograms presented in this report did not show the entire separation and thus it was not possible to assess the potential of this method to resolve other flavonoids.

Increased resolution of flavonoids using the CZE mode has been demonstrated by incorporating an organic modifier into the separation buffer [48]. McGhie and Markham [48] separated 30+ flavonol (aglycone and glycoside form) standards, using a separation buffer containing 20% methanol. The addition of organic to the separation has several effects. Inclusion of an organic resulted in decreased viscosity, lowered the zeta potential of the capillary wall and increased selectivity. Thus while separation times were longer due to decreased electroosmosis, the resolution was greater. The method reported by McGhie and Markham [48] was not applied to the analysis of wine.

2.4. Micellar electrokinetic chromatography separations

The MEKC technique has been used by several investigators for the separation of phenolics from a variety of sources [37,38,42,49,50]. Ferreres et al. [49] used MEKC to analyze the profile of flavonoids in honey as affected by botanical source. These separations were conducted on extracted samples and contained 10% methanol in addition to the surfactant and buffer. This illustrated the potential of the separation method to resolve several polyphenolic antioxidants in a heterogenous mixture.

Work performed in this laboratory has focused on application of the MEKC method for the analysis of resveratrol in wine. The conditions used to obtain the separation shown in Fig. 1, were optimized for the resolution of *trans* and *cis* resveratrol in SPE samples. These variations included buffer composition, pH, and voltage. It was found that *trans*- and *cis*-resveratrol were more readily separated from other constituents with borate–phosphate buffers at pH 9.2, containing 15% acetonitrile (Fig. 2). Increasing the voltage to 25 kV also resulted in higher separation efficiency and shorter analysis time. Under these conditions, the analysis time was reduced to 10 min, which included a 2-min pre-rinse of the capillary [42]. This procedure had a 10-fold lower limit of detection (0.2 μM) for resveratrol than the previous direct injection method.

The method of Gu et al. [42] was subsequently used to analyze wine samples selected from three states in the USA and seven other countries. A total of 26 wines in all were analyzed by the SPE–MEKC procedure. The concentration of *trans*-resveratrol found in this study, ranged from 0.987 to 25.49 μmol/l, while the concentration of *cis*-resveratrol was much lower (Table 2). For most wines, the content of *cis*-resveratrol was about one-third that of *trans*-resveratrol. However, *cis*-resveratrol was not detected in all wines.

3. MEKC separation of other flavonoids

While resveratrol is an important constituent of wine, it represents only a portion of the total number of compounds that have antioxidant activity and

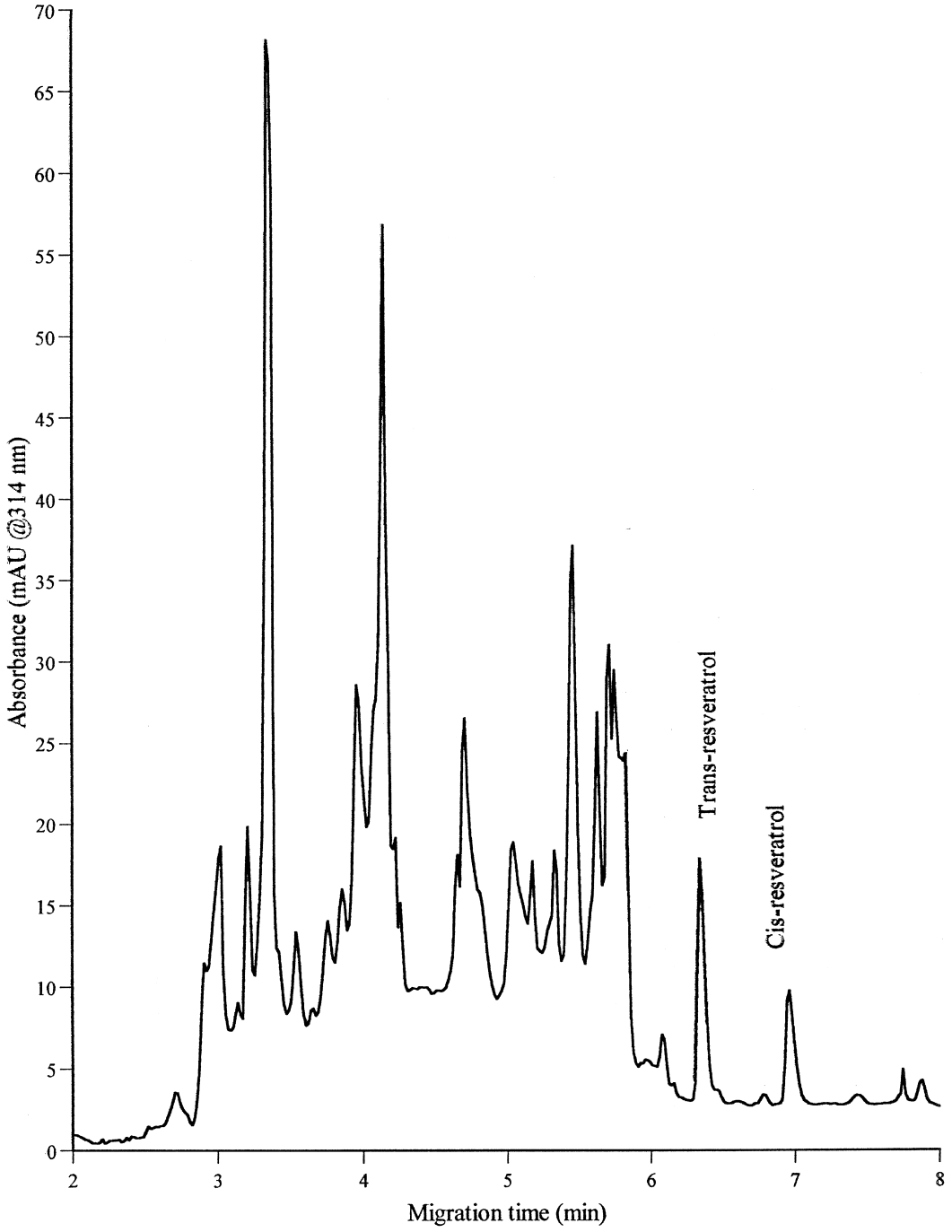

Fig. 2. MEKC separation of red wine after SPE. Electrophoretic separation of red wine was performed with a Beckman P/ACE 5510 equipped with a diode array detector. The capillary was fused-silica [37 cm (30 cm to detectable aperture)×50 μm I.D. The separation was performed in 75 m*M* SDS, 30 m*M* boric acid, 30 m*M* dibasic phosphate, 15% acetonitrile, pH 9.2, at 25 kV and 20°C. Samples (1.0 m*M* in acetonitrile) were injected by application of low pressure (0.5 p.s.i.; 1 p.s.i.=6894.76 Pa) for 3 s. Detectable wavelengths were from 200 to 400 nm. The position of *trans*- and *cis*-resveratrol peaks are identified in the separation.

Table 2
Resveratrol concentration in red wine[a]

Variety or name	Maker	Vintage	*Trans*-	*Cis*-	Total
California					
Cabernet	J. Lohr-Cypress	1994	2.41±0.16	ND	2.41
Zinfandel	Karly-Pokerville	1996	3.26±0.08	ND	3.26
Cabernet Sauvignon	Sutter Home	1995	1.73±0.09	ND	1.73
Special Reserve Red	Mountain View	No Vintage	10.16±0.57	4.29±0.13	14.45
Cabernet Sauvignon	Hawk Crest	1995	1.90±0.29	0.65±0.01	2.56
Merlot	Saintsbury	1996	1.90±0.13	0.68±0.10	2.58
Pinot Noir	Parducci	1996	7.93±0.26	2.44±0.07	10.37
Cabernet Sauvignon	Frey Mendocino	1995	0.99±0.10	ND	0.99
Oregon					
Pinot Noir	Bethel Heights	1996	25.49±2.34	ND	25.49
Washington					
Merlot	Paul Thomas	1995	11.78±0.38	3.34±0.07	15.12
France					
Cotes-Du-Rhone	George Duboeuf	1993	7.62±0.62	1.18±0.07	8.79
Beaujolais Villages	George Duboeuf	1996	6.52±0.16	2.98±0.11	9.50
Bordeaux	Chateau Larose	1994	7.60±0.31	1.66±0.07	9.26
Bordeaux	Christian Moueix	1995	12.71±0.89	2.37±0.15	15.08
Chile					
Merlot	Sunrise-Concha	Toro 1997	5.80±0.29	2.52±0.05	8.32
Cabernet Sauvignon	Castillero del Diablo	1996	4.02±0.16	1.19±0.06	5.21
Spain					
Tinto Reserva Pendes	Mont Marcal	1989	5.66±0.15	0.69±0.02	6.35
Red Navarra	Guelbenzu	1995	10.10±0.27	1.47±0.123	11.57
Australia					
Shiraz	Rosemount Estate	1997	6.78±0.29	2.46±0.08	9.24
Cabernet Sauvignon	Rosemount Estate	1995	6.40±0.29	1.42±0.07	7.82
Argentina					
Cabernet Sauvignon	Santa Julia	1995	5.11±0.37	ND	5.11
Cabernet Sauvignon	Santa Julia	1995	6.78±0.30	ND	6.78
Italy					
Vino Nobile	Montepalciano	1991	2.88±0.20	ND	2.88
Chianti Classico	Castello D'alboa	1995	4.99±0.23	0.83±0.03	5.82
Valpolicella Classico	Zenato	1994	5.06±0.33	0.75±0.03	5.82
Portugal					
Porto	Warre's	No Vintage	2.26±0.10	0.70±0.02	2.95

[a] Values for *trans*- and *cis*-resveratrol represent μ*M* concentrations±SD of the mean of three determinations. ND, not detected. Reprinted with permission from Ref. [42].

perhaps also have health benefits. Specifically, members of this family found in wine include; quercetin, catechin, epicatechin, myricetin, gallic acid, rutin, and kaempherol [39,49]. In addition, piceid and *trans*-astringin (3,5,3′,4′-tetrahydroxystilbene) represent glycosidic forms of resveratrol have not been analyzed by CE. These compounds are of significance because the glycosidic forms may be present at

higher concentration in grape juice or wine than the aglycone form [5,51].

Fig. 3 represents a model separation of several of these target compounds using the same MEKC separation conditions shown in Fig. 2. This separation contains only standards in solution and uses

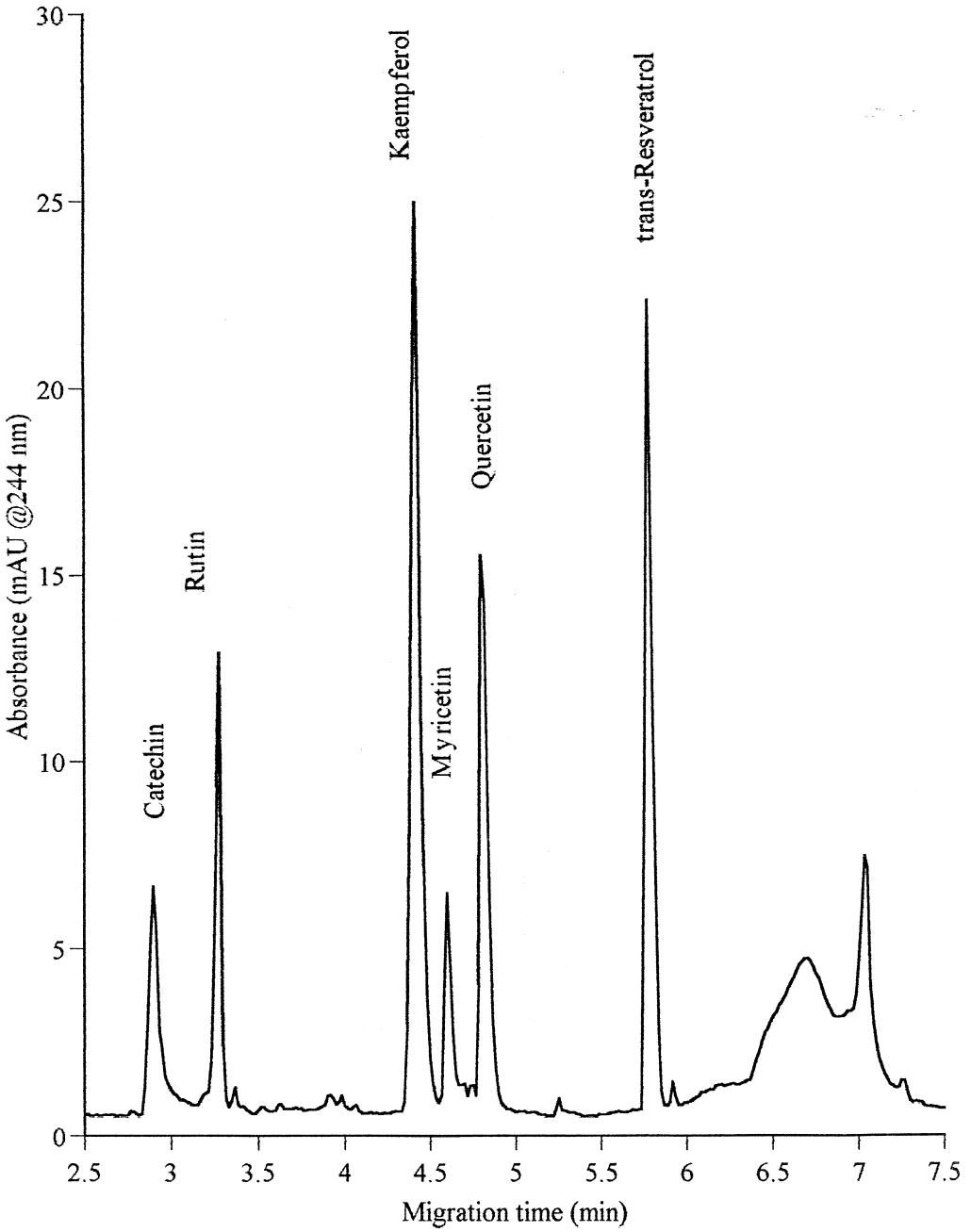

Fig. 3. MEKC separation of flavonoids. Six flavonoid antioxidants, catechin, kaempherol, myricetin, quercetin, rutin, and *trans*-resveratrol, separated under MEKC conditions as described for Fig. 2.

conditions optimized for reseveratrol, however, it serves to illustrate the potential of CE to determine several polyphenolics within the same run. For example, catechin, rutin, kaempferol, myricetin, quercetin and *trans*-resveratrol were separated in less than 6 min. Most likely, it will not be possible to resolve this many compounds in a single run, using a wine sample.

3.1. Future directions

CE is a relatively new and rapidly evolving separation technology. The wide variety of techniques and modes of separation available in CE make it an excellent alternative for the analysis of many compounds found in food such as; amino acids, peptides, proteins, carbohydrates, fatty acids, vitamins, etc. [52]. CE is particularly well suited for the separation of small molecules and has demonstrated the ability to resolve positional as well as optical isomers.

Our experience in developing CE methods for the analysis of antioxidants in wine suggests that several recommendations could be made in regard to sample preparation and separation mode. First, the SPE of wine is very desirable because of the resultant concentration and clean up of samples. Sample concentration can be a factor limiting the sensitivity of CE because injection volumes are very small (nanoliters) and the narrow diameter of the capillary results in a short light path. SPE of wine samples reduces ionic strength, deceases viscosity and facilitates adjustment to running buffer. In addition, elution of the analytes from the SPE cartridge in nonpolar solvent could be used to produce a stacking effect that would further enhance resolution. All of these factors contribute to achieving higher separation efficiency. The time required to perform SPE could be significantly reduced by using small (0.1 g C_{18}) SPE cartridges. These devices would use only 100–200 μl of wine and the subsequent steps of washing, elution(ethyl acetate) and drying, would be faster.

The second major recommendation concerns the mode of separation. The MEKC approach is arguably a more powerful mode of separation than CZE for neutral antioxidant molecules. In MEKC, the partitioning effect provides additional selectivity in the separation [36]. There are a number of surfactant compounds to choose from for the purpose of modulating selectivity. In general, greater selectivity can be achieved through more interaction with the micelle [53]. In the case of flavonoids, SDS is one of the better suited surfactants based on its migration factor k' (analogous to capacity factor in chromatography). The separation efficiency of MEKC can be further improved by inclusion of an organic modifier (acetonitrile used in work presented here). The incorporation of organic solvent increases the relative difference between micelle and electroosmotic front elution times, resulting in increased analyte resolution [53]. Other surfactants such as deoxycholate perform well in micellar separations but, may be better suited for analytes with greater nonpolar character [54]. For selection of surfactant for a particular analyte, the reader is referred to the work of Trone and Khaledi [55]. In summary, the MEKC method has excellent potential to perform separations in which several antioxidants (e.g. glycosides and aglycones) are analyzed in the same run.

Finally, CE technology is rapidly evolving and new modes of separation are being developed. For example, a hybrid technique combining solid-phase materials (C_{18}) with high voltage electrophoresis (called capillary electrochromatography or CEC) is now emerging. Similarly, new devices that can perform high efficiency separations, in very short time frames (seconds) on postage stamp sized silica chips are being reported. The effect of this miniaturization will ultimately result in increased through-put [56].

4. Conclusions

CE has been used by several investigators to determine the level of *trans*- and *cis*-resveratrol in wine samples with good sensitivity, speed, and reproducibility. Most of the CE methods for measuring resveratrol in wine were able to reliably detect resveratrol at 0.2–1.0 μ*M* levels. The technique in its various forms has also been shown to resolve other flavonoids that are present in wine. The levels of resveratrol in these samples determined by our protocol, were similar to those reported using other methodologies (Table 2). Thus this work illustrates

the potential application of CE for the analysis of resveratrol in wine. Improved analysis of flavonoid compounds in wine via CE might be gained by applying SPE to samples, followed by MEKC separation using an organic modifier to vary selectivity.

Acknowledgements

This research was supported by USDA project number 16-069.

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