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REVIEW ARTICLE

A critical review of analytical methods for determination of curcuminoids in turmeric

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Abstract Turmeric (*Curcuma longa*) is one of the most important ingredients in Indian and Chinese cuisine. Curcuminoids and volatile oils present in turmeric are known for their functional and nutraceutical properties. Health benefits attributed to curcuminoids have resulted in their wide utilization in food and pharmaceutical formulations. Therefore, characterization and estimation of the curcuminoids in fresh/dry turmeric, food and nutraceutical products are essential for their quality control during processing and storage. To meet the demand for analytical methods of curcuminoids, several methods have been developed for their quantification in turmeric powder and food formulations. In the present review, various analytical methods (spectrophotometric, chromatographic, capillary electrophoresis and biosensor techniques) which are used for monitoring curcuminoids have been thoroughly summarized and discussed. The spectrophotometric method is not useful when individual components of curcuminoids are required. Mobile phase optimization, the broadness of spots, plate-to-plate variations are significant limitations for TLC and HPTLC methods. Many analysts believe that HPLC method is the best choice for curcuminoids determination because of its rapid analysis. Spectrofluorimetry and Electrochemical methods are the more advanced methods with high sensitivity as well as rapid analysis. However, the selection of analytical method for curcuminoids analysis depends on the type of sample matrix, purpose of the analysis and limit of detection and limit of quantitation of the method.

Keywords Turmeric · Curcuminoids analysis · Analytical methods · Quality control · Review

Introduction

Natural products from plant sources form the basis for many widely used nutraceuticals and functional foods (Nelson et al. 2017). Turmeric (*Curcuma longa*) is one of the most studied plant materials because of its promising health benefits. It belongs to the *Zingiberaceae* family. Tropical and subtropical parts of Asia and Africa are ideal places for its growth and cultivation (Priyadarsini 2014). Turmeric is being used in Ayurvedic medicines since ancient times for the treatment of diabetes, cough, anorexia and sinusitis (Jayaprakasha et al. 2005; Nelson et al. 2017). Furthermore, turmeric is also used as the main ingredient in various food preparations to impart characteristic color and flavor and it acts as preservative as well (Jayaprakasha et al. 2005).

The importance of turmeric mainly comes from its major phytochemical constituents, called curcuminoids. Curcuminoids content of turmeric varies between 2 and 9% based on its cultivar, soil and climatic conditions (Priyadarsini 2014). Curcuminoids mainly contain three chemically related components called as curcumin (C), demethoxycurcumin (DMC) and bis-demethoxycurcumin (BDMC) (Nelson et al. 2017; Meng et al. 2018). The chemical structure of these components is shown in Fig. 1. These three curcuminoids along with other components imparts the distinctive yellow color to the turmeric and turmeric extracts (Jayaprakasha et al. 2005).

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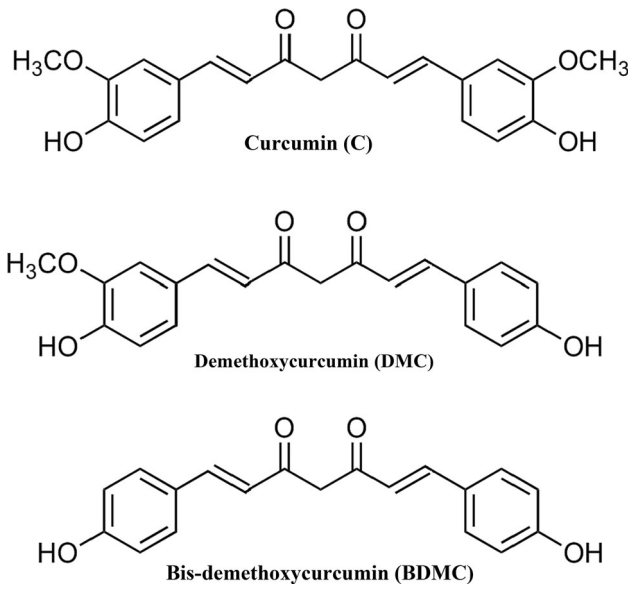

Fig. 1 Structures of curcuminoids

Among the curcuminoids, C is the most abundant, potent, and has been extensively explored for its functional and nutraceutical activities. However, new reports have revealed that DMC and BDMC also had similar or purportedly higher bioactive potential when compared to C (Peram et al. 2017). For example, in case of anticancer activities, BDMC is most potent compared to DMC and C (Ali et al. 2014). Furthermore, it is reported that a mixture of three curcuminoids (in a particular ratio) is more potent than individual curcuminoids, thereby, suggesting the possible synergistic effect (Peram et al. 2017). Although the curcumin was isolated from the turmeric two centuries ago, it is still attracting researchers from all over the world because of its functional properties (Priyadarsini 2014).

Several studies showed that curcuminoids possess different functional and nutraceutical activities, including antioxidant, anticarcinogenic, antidiabetic and hypocholesteremic activities (Rao et al. 1970; Meng et al. 2018). As a result, turmeric has an ever-increasing demand for food, cosmetics, and pharmaceuticals. Many food companies are manufacturing various turmeric products in the form of extracts, powders, coloring agents, food supplements and drinks (Peram et al. 2017). Thus, nowadays, many researchers are trying to develop different functional and therapeutic foods with curcuminoids as an ingredient (Li et al. 2014a). Consequently, government institutions have established regulations for quality control of curcuminoids in finished products. For example, the maximum allowed curcumin in smoked fish is 0.1 g/kg, savory snack (0.1–0.2 g/kg), mustard, sauce, and seasoning (0.3–0.5 g/kg) in Europe (Lee and Choung 2011).

WHO has announced recommendations for quality control of herbal medicines, to ensure the identification of plant materials, purity and content (Baghel et al. 2017). Inevitably, characterization and quantification of three curcuminoids in turmeric powder or food products is essential for its quality control during processing and storage.

Several analytical methods have been developed for the detection of curcuminoids and each method has certain advantages and limitations as well (Cheng et al. 2010; Taha et al. 2015; Kadam et al. 2013; Dey et al. 2018). For example, the spectrophotometric method can only give total curcuminoids content whereas other advanced methods can simultaneously quantify each curcuminoid (Kadam et al. 2013). Therefore, selection of analytical method is crucial for obtaining better results. There are many critical reviews available on chemical, biological and pharmacological properties of curcuminoids. However, reviews on different analytical methods of curcuminoids are extremely limited. Therefore, the authors wish to give a flavor of some of the analytical methods for the determination of curcuminoids in turmeric and food formulations. It is hoped that this will encourage the general readers to select a suitable analytical method for specific requirements.

Spectrophotometric methods

UV–Vis spectrophotometry

The spectrophotometric method is simple and most commonly used method for the determination of curcumin in various sample matrices (Jayaprakasha et al. 2002). Methanol was found to be a suitable solvent for spectrophotometric measurements of curcumin in most of the sample matrices (Kadam et al. 2013). However, in this method, precision is low due to other color interfering pigments present in the sample (Pathania et al. 2006). Moreover, this method does not give the relative composition of individual curcuminoids, which is a major limitation for this method (Rohman 2012). Taylor and McDowell (1992) compared spectrophotometric and HPLC methods and reported that the spectrophotometric method had shown more curcumin content than HPLC method in turmeric rhizomes which is due to the fact that non-curcumin components were also absorbed at the same wavelength as curcumin.

To overcome this problem, a first-order differentiation of spectrum is performed, since it provides greater resolution. As a result, it is possible to analyze each component in the presence of other elements without any pretreatment or interference (Dave et al. 2007). Pundarikakshudu and Dave (2010) used first-order differential spectrophotometry

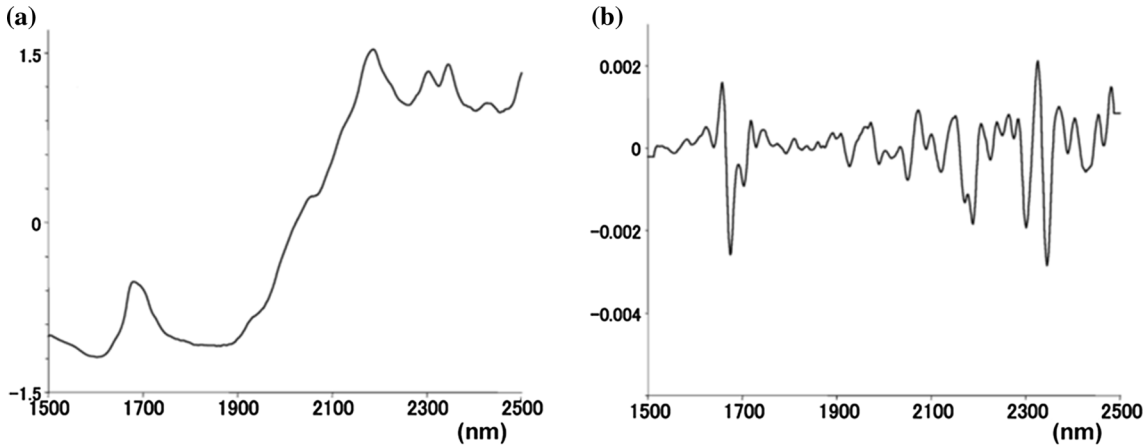

Fig. 2 **a** Near IR spectra of demethoxycurcumin and **b** second order differential spectra of demethoxycurcumin (Tanaka et al. 2008)

for simultaneous determination of berberine and curcumin in combined methanolic extracts of *Berberis aristata* and *Curcuma longa* without any prior separation or purification step. Few other researchers used the extinction coefficient as a basis for analysis of curcuminoids using spectrophotometric method (Scotter 2009). The Joint Expert Committee on Food Additives (JECFA) prescribed that absorbance for curcumin in ethanol to be at 425 nm when determined by a spectrophotometric method of an assay with corresponding extinction coefficient $E^{1\%}_{1\,\mathrm{cm}} = 1607$ as a reference value for the three curcuminoids together (Rohman 2012). From the above information, it is clear that spectrophotometric methods are useful when individual curcuminoids concentration is not a necessary quality parameter (Kadam et al. 2013).

Infrared (IR) Spectroscopy

IR spectroscopy is the preferred method for the qualitative and quantitative analysis of physiologically active ingredients in food compositions (Kar et al. 2018). The primary mechanism involved in this method is arising of overtone and combination bands form fundamental chemical vibrations (Kasemsumran et al. 2014). This method can be combined with the chemometric tools, which could be used for analysis of food products both qualitatively and quantitatively. As a result, this technique allows fast, nondestructive analysis with minimal or no sample preparation and without the use of any chemical reagents (Roggo et al. 2007). Few researchers reported that IR spectrometry methods for determination of curcuminoids directly in turmeric powder and in some food formulations (Tanaka et al. 2008; Kim et al. 2014). The IR bands usually overlap and results into spectrum with broad peaks. However, IR spectra generally contain a significant amount of information about the molecular and physical structure of the sample. Thus, various multivariate statistical data analysis tool can be employed to extract the meaningful result. Tanaka et al. (2008) studied the profile of curcuminoids in 34 samples of turmeric using near infrared (NIR) spectroscopy and multidimensional statistics. Two characteristic absorptions of curcuminoids were detected in the second derivatives of the NIR spectra (Fig. 2) of turmeric samples and are around 1700 and 2300–2320 nm. Using Partial least-squares regression (PLS) method, they quantified curcuminoids content in turmeric sample. Although this technique is rapid and nondestructive, many samples from different sources are required to create a strong PLS model (Kasemsumran et al. 2014). Despite this, IR spectroscopy is suitable for quality control purpose in food industries due to its rapid and nondestructive nature of analysis.

Chromatographic methods

Thin layer chromatography (TLC) and high-performance thin layer chromatography (HPTLC)

Chromatography is a technique used for the separation of closely related components in a mixture by differential migration through immiscible stationery and mobile phases (Jupille and Perry 1977). Thus, successful separation of individual components of curcuminoids (C, DMC, and BDMC) by TLC method is possible using an optimized mobile phase. Janben and Gole (1984) were the first to report separation of curcuminoids in spices using chloroform:acetic acid (80:20 v/v) and silica gel 60 thin layer plates as mobile and stationary phases, respectively. They also determined curcuminoids content in spices by measuring the intensity of rubrocurcumin on the layer, which was obtained by treating boric-acetic acid reagent with curcumin. Few other authors also reported the TLC method

Table 1 TLC and HPTLC methods for determination of curcuminoids

Sample	Stationary phase	Mobile phase	Solvent[a]	Wavelength	LOD and LOQ	References
TLC methods						
Turmeric powder	Silica gel	$CHCl_3$:CH_3COOH (80:20)	CH_3OH	436 nm	Not reported	Janben and Gole (1984)
Turmeric rhizomes	Silica gel plate 60F254	C_6H_{14}:$CHCl_3$:CH_3OH (10:10:1 v/v/v)	CH_3OH	254 nm	43–73 and 43–242 ng/spot	(Sotanaphun et al. (2009)
Turmeric rhizomes	Silica gel plate 60 F254	$CHCl_3$:C_6H_{14}:CH_3OH (1:1:0.1 v/v/v)	CH_2Cl_2	Image analysis	LOD: 158 and LOD: 525 ng/mL	Phattanawasin et al. (2009)
HPTLC methods						
Turmeric rhizomes	LiChrosphere aluminium plates SI 60F254	$CHCl_3$:CH_3OH (98:2 v/v	C_3H_6O	366 nm	LOD: 40 and LOQ: 100 ng/mL	Pathania et al. (2006)
Turmeric rhizomes	Nano Silica gel 60F 254	$CHCl_3$:$C_4H_8O_2$ (19:1 v/v)	C_2H_6O	254 and 366 nm	Not reported	Green et al. (2008)
Turmeric rhizomes	Silica gel aluminum plate 60GF254	$CHCl_3$:CH_3OH (48:2 v/v)	C_6H_6	425 nm	LOD: 0.1 µg/spot	Paramasivam et al. (2009)
Turmeric powder	Silica gel 60 F254	CH_2C_{12}:CH_3OH (99:1) combination	CH_3OH	427 nm	LOD: 49 and LOD: 148 ng/mL	Gantait et al. (2011)
Turmeric rhizomes	Silica gel plate 60 F254	C_7H_8:$C_4H_8O_2$:CH_2O_2 (9:6:0.4)	C_2H_6O	200 and 700 nm	Not reported	Taha et al. (2015)
Polyherbal formulation	Silica gel aluminum plate 60 F254	C_7H_8:$C_4H_8O_2$:CH_2O_2 (4.5:4:0.1, v/v/v)	CH_3OH	250 nm	Not reported	Baghel et al. (2017)

[a]Used in sample preparation

(with many modifications) for separation and quantification of curcuminoids (Phattanawasin et al. 2009). Although the TLC method has some advantages (low cost, easy maintenance, and selectivity), its usage has gradually declined due to prolong separation time and poor resolution in the case of turmeric analysis. HPTLC method can overcome these limitations. It works on the same principle of TLC, but some changes have been made to increase resolution and to allow low detection levels like use of finer particles on the stationary phase of TLC plates and improved image scanning. Several HPTLC methods have been reported to determine curcuminoids as a single component or combination with others in turmeric and processed products. Those methods are detailed in Table 1.

HPTLC is one of the extensively used chromatographic techniques for quality analysis of food products because of its advantages. For instance, this is the only chromatographic method which gives results as an image (Attimarad et al. 2011). In addition to this, less solvent consumption, offline method and less warm up time for instrument to get ready for experimentation, makes the technique more beneficial when compared to HPLC (Ansari et al. 2005; Pathania et al. 2006). Methanol was found the most suitable solvent for maximum extraction of curcuminoids in HPTLC sample preparation (Paramasivam et al. 2009). Developing optimum mobile phase is the hardest part in HPTLC separation. Usually, it is a trial and error process. Ansari et al. (2005) first tried methanol:chloroform (0.5:9.5 v/v) which resulted in good results however typical peak nature was missing. Finally, a sharp, well-defined peak (Fig. 3) was provided by the mobile phase consisting of methanol:chloroform (0.75:9.25 v/v).

The HPTLC chamber should be saturated with the mobile phase before experiment for clear spots on TLC plates (Ansari et al. 2005). The broadness of spots is the major problem in HPTLC method. Pathania et al. (2006) improved the HPTLC method by using LiChroshere plate that overcame the difficulties of the broadness of the spots. Limit of detection and variation from plate to plate are the

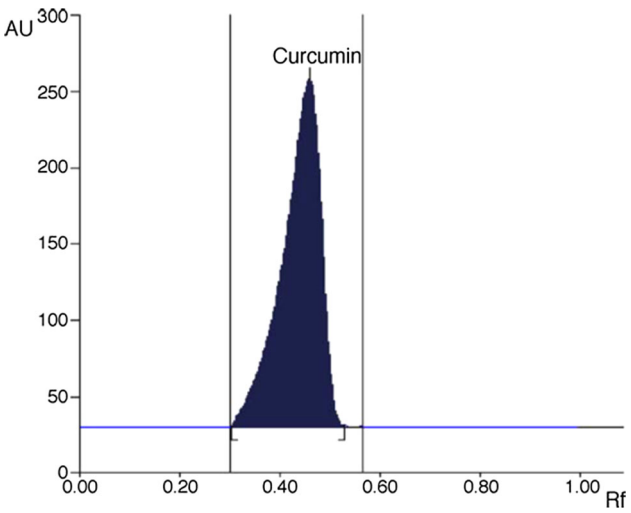

Fig. 3 A typical HPTLC chromatogram of curcumin (Rf = 0.48) (Ansari et al. 2005)

main controlling aspects for the use of HPTLC method. However, these limitations can be overcome by pointing known amount of standard together with the unknown sample in each experiment (Pathania et al. 2006). Paramasivam et al. (2009) used the HPTLC method to find high-quality turmeric plant concerning curcuminoids. This method could be used for identifying high-quality turmeric cultivars for plant breeding program. Gantait et al. (2011) compared curcuminoids content in several market samples and in-house turmeric powder using HPTLC method and reported that turmeric powder available in market has less curcumin (LOD: 49 ng/ml; LOD: 148 ng/ml).

High-performance liquid chromatography (HPLC)

There are many HPLC methods to determine curcuminoids in turmeric and processed products, which are summarized in Table 2. Separation and quantitation of components in a mixture are the main properties of HPLC systems. These properties of HPLC overcome the drawbacks of the spectrophotometric method, which cannot quantify the individual components of curcuminoids. Since curcuminoids are thermally liable and less volatile in nature, separation and quantifying them with gas chromatography is also not popular (Rohman 2012). Although separation and quantification of curcuminoids are possible with TLC methods, these methods could not resolve curcuminoids completely. Figure 4 shows the schematic view of curcuminoids separation in C18 column and typical chromatogram of standard curcuminoids mixture. Inevitably, many analysts believe that HPLC method is the best choice for curcuminoids determination because of its rapid analysis and accuracy. In curcuminoids analysis, HPLC together with UV–VIS or photodiode array detector (PAD) are the routine methods (Jadhav et al. 2007). Tonnesen and Karlsen (1983) were the first to employ this method for estimation of curcumin and its related components. Jayaprakasha et al. (2002) modified the existing HPLC protocol with gradient elution of a solvent mixture of acetonitrile, methanol, and acetic acid for the determination of curcuminoids with a run time of 20 min.

In the HPLC method, the food matrix is an essential factor that affects the extraction efficiency of curcuminoids in food samples. Lee and Choung (2011) reported recovery rates of 16 food types. Among these, solid foods showed the highest recovery rates (above 90%) whereas beverages and some other liquid foods showed less than 3.3%. In any analytical method, extraction of target components from the sample matrix is the most critical step. For extraction of phenolic, the solvent type has a unique role even though other factors (e.g., particle size, pH, solute to solvent ratio and temperature etc.) also effect the efficiency of extraction (Lee and Choung 2011). In the case of curcuminoids extraction, methanol was found to be an appropriate solvent (Paramasivam et al. 2009). Lee and Choung (2011) compared three different solvents (ethyl acetate, acetonitrile, and methanol) for extraction of curcuminoids and reported methanol followed by acetonitrile and ethyl acetate showed better efficiency in isolation of curcuminoids from the sample matrix. C, DMC, and BDMC are powerful complexing agents; they can form inter and intera molecular bonds. Therefore, separation in chromatographic methods entirely depends upon the bonding between a reactive di-ketone group of curcuminoids and stationary phase. Usually, some interaction is necessary between curcuminoids and stationary phase to get successful separation (Jadhav et al. 2007; Mudge et al. 2016; Peram et al. 2017). Due to the liable characteristics of curcuminoids, mostly, C-18 columns are preferred for determination of curcumin using HPLC systems. However, for better separation with this column, pH must be very low which damages the column in the long run. Moreover, the temperature of the column has to be maintained for the peak shape and low retention time of the curcuminoids (Mudge et al. 2016; Peram et al. 2017). Usage of other types of columns were also reported, for example, RP-5NH_2 (Khurana and Ho 1988) TSK-GEL ODS 80 TS (Inoue et al. 2008) and Chromolith column (Malasoni et al. 2013), but these columns do not show any advantage compared to those of C18 columns. For the first time, (Ali et al. 2014) used a phenyl column for resolving curcuminoids, and their results showed that this column is beneficial, as it can successfully separate curcuminoids at normal temperature, works under the acid-free condition and has better performance. Type of stationary phase and specific surface area are major factors that will affect separation of curcuminoids(Jadhav et al. 2007). Major indicators for poor separation of curcuminoids are elevation of the baseline along with broad tailing of peaks (Peram et al. 2017). The mobile phase is an important factor that affects the separation process in the HPLC system. Gradient elution mobile phase has shown better separation when compared to that of isocratic elution mobile phase. Due to the hydrophilic nature of curcuminoids, HPLC separation is mostly done on reverse phase (RP) silica phases using a mixture of water, acetonitrile, ethanol, and methanol (Jayaprakasha et al. 2002; Jadhav et al. 2007; Naidu et al. 2009). Several authors reported that addition of formic acid (0.1%) to water resulted in sharp and well-defined peaks (Peram et al. 2017). However, gradient elution mobile phase is a very complex mix of different solvents and need more experimentation to find the optimized combination (Naidu et al. 2009).

Recently many improved HPLC methods, which are validated as per the guidelines of International Conference on Harmonization (ICH), are reported (Wichitnithad et al.

Table 2 HPLC and LC–MS/MS methods for determination of curcuminoids

Sample matrix	Mobile phase	Column and detector	Separation time (min)	LOD and flow rate	Reference
HPLC methods					
Turmeric powder	C_2H_5OH:H2O (96:04 v/v)	RP-5-NH_2, UV 280 nm	20.73	–; 1 mL/min	Khurana and Ho (1988)
Fresh turmeric extract	(A) H_2O (0.25% CH_3COOH) and (B) CH_3CN, 0–17 min, 40– 60% B; 17–32 min, 60–100% B; 32–38 min, 100% B; 38–40 min, 100–40% B	C18, UV 200–500 nm	14.0	–; 0.2 mL/min	He et al. (1998)
Turmeric and spent oleoresin	CH_3OH–2% CH_3COOH– CH_3CN	C18, UV 425 nm, UV 425 nm	6.75	0.05 µg/mL, 1 mL/min	Jayaprakasha et al. (2002)
Turmeric powder	CH_3CN–0.1% CF_3COOH– (50:50 v/v), (pH adjusted to 3.0 with NH_3)	C18, UV–VIS 420 nm	9.0	27.99, 31.91 and 21.81 ng/mL for C, DMC and BDMC; 1.5 mL/min	Jadhav et al. (2007)
Turmeric extracts	Isocratic elution of CH_3CN and 2% v/v CH_3COOH (40:60v/v)	RP-Alltima C18 Column	13.6	0.90, 0.84, 0.08 µg/mL for C, DMC and BDMC; 2.0 mL/min	Wichitnithad et al. (2009)
Turmeric powder and tablet	0.1 M of acetate buffer (pH 4.0)–CH_3CN (57:43 v/v)	C18, fluorescence detector RF-10A_{XL}	~28	1.5, 0.9 and 0.09 ng/mL for C, DMC and BDMC; 1 mL/min	Zhang et al. (2009)
Turmeric oleoresin	C_3H_8O:H_2O (95:05 v/v)	Exil-Amino column, UV–VIS 425 nm	11	0.3 µg/mL; 1 mL/min	Naidu et al. (2009)
Curcuminoids-loaded liposome	1% H_3PO_4–CH_3CN	C18, UV–VIS 425 nm	6.36	2.5 mg/mL; 1.0 mL/min	Jangle and Thorat (2013)
Turmeric powder	ACN–MeOH–H_2O (40:20:40 v/v	RP-phenyl column, UV–VIS	10.5	0.30–0.50 ng/mL; 1.0 mL/min	Ali et al. (2014)
Turmeric powder	10 mM Na_2HPO_4:H_3PO_4 (pH 5.0) (50:50 v/v)	C18, Electrochemical detection cell	15.0	0.208, 0.197 and 0.227 µM for C, DMC and BDMC; 1.0 mL/min	Long et al. (2014)
Turmeric colour pigments, curry powder	CH_3OH (A):C_4H_8O (B): 0.1 g/100 ml H_3PO_4 in H_2O (C). Gradient system: 0–15 min, 10–15% A, 30–40% B, and 60–45% C; 15–20 min, 15–55% A, 40–10% B, and 45–35% C	C18, UV 425 nm	17.13	0.27, 0.18, 0.23 µg/mL for C, DMC and BDMC; 1.0 mL/min	Li et al. (2014b)
Turmeric extract and emulsion	CH_3CN:CH_3OH:H_2O (40:20:40 v/v/v)	C18, UV/VIS detector	6.67	0.305 µg/mL; 1.5 mL/min	Syed et al. (2015)
Turmeric rhizome	Acetonitrile:water (70:30 v/v).	C18, DAD	15.08	1.0 µg/mL; 0.8 mL/min	Hwang et al. (2016)
In different commercial products	0.1% CH_3COOH in H_2O(A): CH_3CN with 0.1% CH_3COOH (B) Gradient Program:0 min,45% of solvent B; Step 1: 1.5 min, 65% solvent B; Step 2: 2.5 min, 90% solvent B; Step 3: 4.0 min, 90%	C18, Photodiode array detector	1.3	0.40, 0.20, 0.19 µg/mL for C, DMC and BDMC 2.5 mL/min	Osorio-Tobón et al. (2016)
In different commercial products	CH_3CN: 0.1% CH_2O_2 in H_2O	C18, Photodiode array detector	9.18	7.40, 9.24 and 6.48 ng/mL for C, DMC and BDMC; 0.8 mL/min	Peram et al. (2017)
Java turmeric	Gradient elution, acetonitrile- 0.001% formic acid	Phenomenex C18, UV–VIS 425 nm	10.72	0.0250, 0.0166, 0.0119 µg/mL for C, DMC and BDMC;1 mL/min	Erpina et al. (2017)

Table 2 continued

Sample matrix	Mobile phase	Column and detector	Separation time (min)	LOD and flow rate	Reference
LC–MS/MS methods					
Equine plasma	0.1% (v/v) CH_2O_2 in C_2H_3N (A) and 0.1% (v/v) CH_2O_2 in H_2O (B); isocratic program (43% A: 57% B)	XBridge BEH C18, MS, electrospray ionization	9	1 ng/mL; 0.2 mL/min	Liu et al. (2018b)
Bacterial culture medium	10 mM $C_2H_7NO_2$ and 0.1% (v/v) CH_2O_2 in H_2O (A) or in acetonitrile (B). Gradient elution: 0–5 min, 20% B; 5–8.1 min, 80% B; 8.1–10.0 min, 20% B.	Poroshell 120 EC-C8 column , MS, electrospray ionization	10	0.1 µM; 0.3 mL/min	Tan et al. (2015)
Turmeric rhizome	5 mM NH_4HCO_2, 0.1% CH_2O_2, in H_2O (A); C_2H_3N (B); Gradient (in buffer A): 0–2 min, 5% B; 2–57 min, 5–100% B; 57–60 min, 100% B; 60–65 min, 100–5% B; 65–75 min, 5% B	Discovery HS C18; MS Sustained off-resonance irradiation fragmentation (SORI)	75	–; 0.25 mL/min	Jiang et al. (2006a)
Plasma samples	10.0 mM NH_4HCO_2 (pH 3.0) (A) and CH_3OH (B) Gradient elution: 0–3.0 min (25–90% B), 3.0–7.50 min (90–90% B), 7.50–7.51 min (90–25% B), 7.51–11.0 min (25–25% B)	Xterra MS C18, MS, electrospray ionization	11.0	2.50–179 ng/mL; 0.25 mL/min	Kunati et al. (2018)
Cell medium and mouse plasma	0.1% CH_2O_2 in C_2H_3N (50%) (A) and H_2O (B); isocratic mode	Beta basic C8 column, MS ion reaction monitoring	12	1 ng/mL; 0.2 mL/min	Vijaya Saradhi et al. (2010)
Human plasma	0.1% CH_2O_2 in C_2H_3N (50%) (A) and H_2O (B); isocratic mode	BetaBasic C8 column, MS, electro-spray ionization	5	2.0 ng/ml; 0.2 mL/min	Chen et al. (2012)

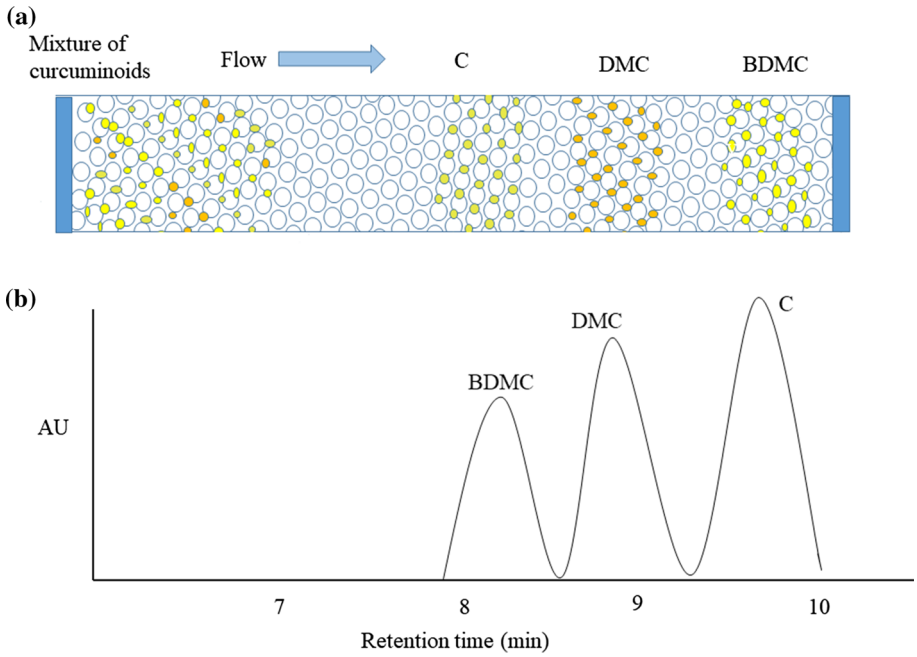

Fig. 4 **a** Separation of mixture of curcuminoids and **b** HPLC chromatograms of the standard mixture of curcuminoids

2009; Ali et al. 2014). Most of the HPLC methods reported in the literature for quantification of curcuminoids had certain limitations such as high flow rates (Osorio-Tobón et al. 2016), long run times (Li et al. 2011), complicated gradient elution (Li et al. 2014a), buffer solutions in mobile phase and high limits of detection (Jangle and Thorat 2013). Besides, these methods are restricted for quantification of curcuminoids in one particular type of turmeric products (Peram et al. 2017). Thus, nowadays researchers are improving HPLC methods for rapid identification, differentiation, and quantification of curcuminoids

(Lechtenberg et al. 2004). However, overcoming all the limitations mentioned above is not achieved yet.

Ultra high-performance liquid chromatography (UHPLC)

Although HPLC method is most convenient among the chromatographic methods for analysis of curcuminoids, there are several limitations to the HPLC approach (discussed in the previous section). For the better performance of chromatographic methods, several improvements have been made to existing technology. As a result, the UHPLC method has become one of the most promising technique in the field of fast chromatography (Taibon et al. 2015). The columns of UHPLC are modified with sub micrometer (sub-2 μm) particles as a stationary phase. These small particles are responsible for the radical increase in resolution per time because the rate of flow of mobile phase and performance of chromatography are inversely related to the size of UHPLC column particles (Jerkovich et al. 2005). Figure 5 shows the comparison of chromatograms of curcuminoids obtained from HPLC and UHPLC methods. Cheng et al. (2010) developed a new RP-UHPLC method and validated according to ICH guidelines. In this report, authors also compared UHPLC with HPLC for different parameters like sensitivity, time of analysis and efficiency. Overall, this method is suitable for quick and accurate quality control of curcuminoids. Avula et al. (2012) used UHPLC-UV–MS method for determination of curcuminoids in turmeric rhizome tougher with C18 column and acetonitrile:water as mobile phase. They achieved clear separation of curcuminoids in the column within 3.5 min only. This proves the method is rapid and accurate for quality control of curcuminoids. Jia et al. (2017) used UHPLC- QTOF –MS/MS (UHPLC quadrupole time of flight tandem mass spectrometry) to analyze curcuminoids in turmeric rhizome. According to them, separation of isomers that belong to the same type of curcuminoids could be done which is not possible by any other chromatographic methods. Although UHPLC method is simple, economical, rapid and most reliable method for analysis of curcuminoids for quality control, there are only a few reports available in the literature about UHPLC application.

Liquid chromatography-mass spectrometry (LC–MS)

Although the above-mentioned methods can determine curcuminoids in turmeric powder or in its processed products, these methods cannot determine very low levels of curcuminoids. In this regard, the LC–MS method is a promising method that can detect very low levels of curcuminoids in any given sample matrix. In this method, LC follows the same principle as in the HPLC, but the coupling of the MS detector to LC makes these methods more efficient as compared to HPLC and HPTLC methods (Pitt 2009). Time-consuming chemical modifications can be eliminated by this method, which permits MS analysis of non-volatile, thermally labile, or charged molecules. A

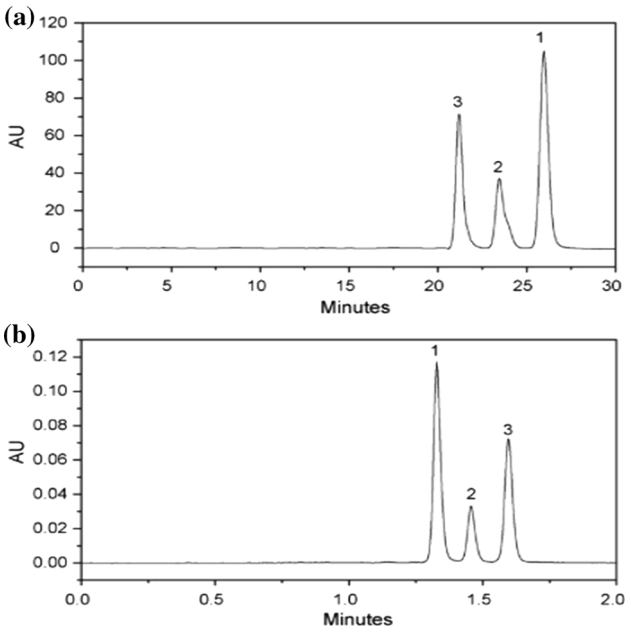

Fig. 5 Comparison of chromatograms of (1) curcumin; (2) desmethoxycurcumin; (3) bis desmethoxycurcumin obtained from **a** HPLC and **b** UPLC (Cheng et al. 2010)

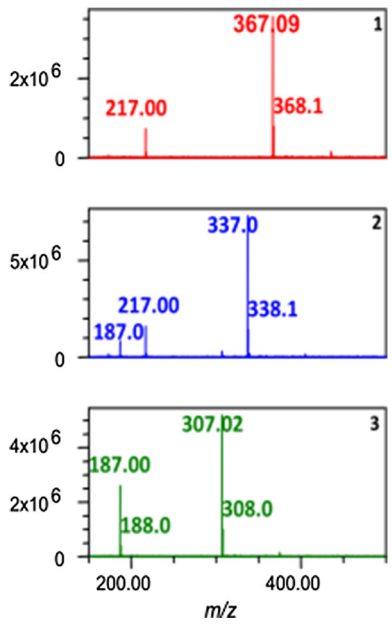

Fig. 6 A typical mass spectrum of an of standard curcuminoids: (1) curcumin, (2) demethoxycurcumin and (3) bis-demethoxycurcumin (Avula et al. 2012)

typical mass spectrum of standard curcuminoids is shown in Fig. 6. He et al. (1998) reported first LC–MS method for analysis of curcuminoids in turmeric rhizome. In this study, they have used electro-spray mass spectrometry and UV-diode-array to analyze curcuminoids however complete structural details were not reported. This is because of using a single dimensional LC–MS method with only one mode of ionization. Thus, using tandem mass spectrometry can overcome this problem. The fragmentation behavior of the three curcuminoids in ion trap LC–MS/MS was investigated by Jiang et al. (2006a) in both positive and negative mode electrospray ionization. They also used to sustain off-resonance irradiation (SORI) in a Fourier Transform Ion Cyclotron resonance (FTICR) mass spectrometer. In this study, the analysis of all three curcuminoids in turmeric rhizome was identified along with other minor curcuminoids, and their origins were given. Jiang et al. (2006b) used LC–ESI–MS/MS coupled to Diode Array Detection (DAD) to identify known and unknown diarylheptanoids in fresh turmeric rhizome extracts, and they identified 12 new diarylheptanoids. Many studies proved that metabolites of curcuminoids also have pharmacological activity similar to curcuminoids (Prasad et al. 2014). Thus, several methods were reported for determining curcuminoids metabolites content along with curcuminoids using LC–MS/MS in biological matrices (Table 2).

Capillary electrophoresis (CE)

Many chromatographic methods are available for the separation and analysis of curcuminoids (discussed in the previous section). Their primary disadvantages are either elaborated sample preparation and highly dependent on the sample matrix, or requirement of sophisticated detectors for analysis, especially in the case of LC–MS/MS. Thus, there is a requirement for more advanced methods, which could allow efficient separation and quantification of curcuminoids in the variety of sample matrices. CE method possesses many advantages such as rapid separation, inexpensive, low solvent and sample requirement for analysis (Sun et al. 2002).The main mechanism of CE is separation of components present in the sample based on different migration properties of electrically charged components through the capillary. The most general set up CE is shown in Fig. 7. It consists of a capillary tube fused with silica and the two ends of capillary tube placed in buffer reservoirs of inlet and outlet. However, there are some disadvantages with CE, such as small injection volume and low detection sensitivity due to the small inner diameter (Wu et al. 2018). For the determination of curcuminoids other CE method such as micellar electrokinetic chromatography (MEKC) and microemulsion electrokinetic chromatography have also been used coupled with different detectors (UV–VIS, PAD, and AD (Amperometric Detector)). Watnabe et al. (2000) developed a fast analysis MEKC method employing a high molecular mass surfactant. However, this method is highly dependent on the commercial availability of the micelle-forming agents. Sun et al. (2002) used the CE method together with AD for the determination of curcuminoids in turmeric samples. They successfully separated and estimated the curcuminoids under optimized conditions. Based on the pattern of curcuminoids, Lechtenberg et al. (2004) differentiated *C. domestic* and *C. xanthorrhiza* verities using CE-PAD method. Maráková et al. (2011) also used the same method with cyclodextrin as a complexing agent. This modification resulted in successful separation of curcuminoids and reduced the absorption of curcuminoids on capillary wall. Li et al. (2014a) observed the degradation of curcuminoids when they come in contact with alkaline buffer which is generally used in CE and MEKC methods. To avoid this problem Nhujak et al. (2006) tried acidic buffer (pH 2.5) in MEEKC method, although alkaline degradation is avoided they found that solubility of curcuminoids is poor in acidic and neutral buffers. Similarly, Li et al. (2014a) used the

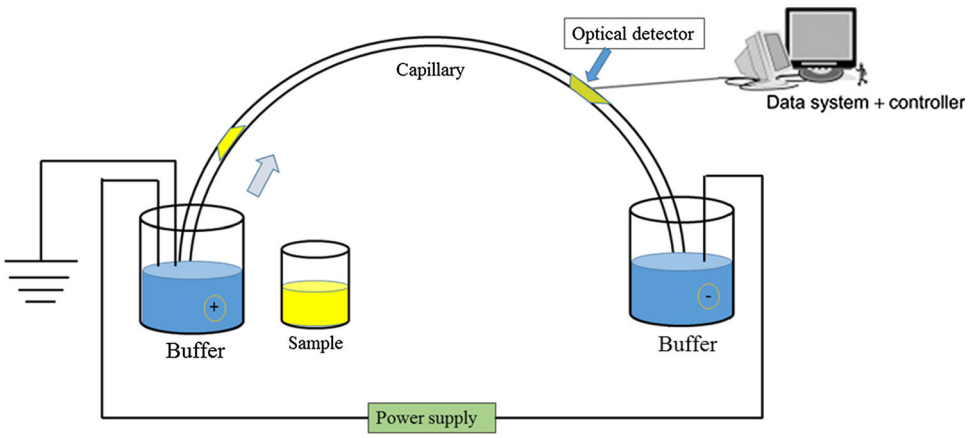

Fig. 7 General schematic view of a capillary electrophoresis system with detector and control unit

Table 3 Spectrofluorimetry and electrochemical methods for determination of curcumin

Sample	Method type	Limit of detection	References
Spectrofluorimetric methods			
Curry powder	Fluorimetric Method using the Enhancement of Mixed Micelle	0.017 ng/mL	Wang et al. (2006)
Drug sample	Fluorescent carbon dots	44.8 ng/mL	Shi et al. (2015)
Urine samples and	Nitrogen-doped carbon dots as fluorescent probe	31.24 ng/mL	Zhang et al. (2015)
Urine	Boron and nitrogen co-doped carbon dots	23.94 ng/mL	Bian et al. (2018)
Drinking water and the food samples	A nitrogen and phosphorus dual-doped carbon dots (NP-C dots)	21.37 ng/mL	Liu et al. (2018a)
Food matrix	Nitrogen and chlorine dual-doped carbon nanodots	14.00 ng/mL	Hu et al. (2019)
Electrochemical methods			
Curcumin standard	Voltammetry-Glassy carbon electrode modified by carbon nanotubes	1.84 ng/mL	Daneshgar et al. (2009)
Multicomponent spices	Voltammetry- glassy carbon electrode	1.51 µg/mL	Ziyatdinova et al. (2012)
Curcumin standard	Cyclic Voltammetry- poly-Acid chrome blue K (poly- ACBK) film is synthesized on the surface of glassy carbon electrode (GCE)	15.10 ng/mL	Peng et al. (2012)
Spice powder	Adsorptive stripping voltammetry- Carbon-Screen Printed Electrodes	1.80 µg/mL	Wray et al. (2012)
Turmeric rhizomes	Voltammetric method- Graphene on Glassy carbon electrode	11.05 ng/mL	Li et al. (2014c)
Turmeric extractive	Voltammetric method- Electrochemically reduced Graphene oxide	36.84 ng/mL	Zhang et al. (2016)
Curcumin in plasma	Ru@Au nanoparticle decorated nitrogen and sulfur-functionalized reduced graphene oxide nanomaterials	0.073 pg/mL	Kotan et al. (2016)

same method with electrically charged liquid as an oil phase which showed protective effects on analytes during analysis. In CE analysis, detectable optical path-length usually is very small (in micrometers), and for this reason, the sensitivity of this method is low if traditional absorbance detectors are used (Swinney and Bornhop 2000). To overcome this problem, Wu et al. (2018)developed the MEKC method coupled with LINF (laser-induced native fluorescence) detection to improve the sensitivity of the CE method. As per their results, LINF detector can sense the lowest level (LOD for C: 4.1; DMC: 2.6; BDMC: 0.4 ng/ml) curcuminoids among other CE detectors.

Biosensors

Biosensor is a compact analytical device consisting of a biological receptor and a physicochemical transducer (Lu et al. 2017). They can facilitate rapid analysis and offer the potential for real-time monitoring and portability. Spectrofluorimetry and Electrochemical detection methods are the two extensively studied biosensor methods for determination of curcumin in various sample matrices which are summarized in Table 3.

Spectrofluorimetry

Spectrofluorimetry is attracting researchers with unique advantages, such as simple and fast analysis, high sensitivity and economical (Zhang et al. 2003). Fluorescent nanomaterials especially, carbon dots (CDs) have been widely used as chem-probe and biosensor due to its numerous advantages (Xu et al. 2016). Although fluorescent CDs have many advantages, their fluorescence quantum yield is low. Nowadays, to improve the optical properties of CDs, doping with heteroatoms such as nitrogen has been tried. However, the results are not promising compared to pure CDs (Ju and Chen 2014). Bian et al. (2018) synthesized boron and nitrogen co-doped CDs (BNCDs) by using microwave heating and citric acid monohydrate as carbon source. They proved florescence intensity BNCDs could be considerably quenched by curcumin. Using this property, they successfully estimated curcumin content in liquid samples. Liu et al. (2018a) synthesized double doped CDs with nitrogen and phosphorus and glucose as the carbon source. They tested the new sensor for detection of low levels of curcumin in aqueous solution which was able to detect very low levels of curcumin (21.37 ng/mL), which was the lowest detectable limit using spectrofluorimetry method till now.

Table 4 Comparison of different analytical methods based on detection limit of curcumin

Method	Lowest detection limit	References
Near-infrared spectroscopy	10 ng/mL	Tanaka et al. (2008)
HPLC-fluorescence method	15 ng/ml	Zhang et al. (2009)
UPLC	40.66 pg/mL	Cheng et al. (2010)
UV–VIS spectrophotometric method	39 ng/mL	Pundarikakshudu and Dave (2010)
LC–MS/MS	1 ng/mL	Vijaya Saradhi et al. (2010)
HPTLC	49 ng/mL	Gantait et al. (2011)
HPLC-electrochemical detection	76.62 ng/mL	Long et al. (2014)
Reversed phase-HPLC phenyl column	0.3 ng/mL	Ali et al. (2014)
micellar electrokinetic chromatography	4.1 ng/mL	Wu et al. (2018)
Ru@Au nanoparticle decorated nitrogen and sulfur- functionalized reduced graphene oxide nanomaterials	0.073 pg/mL	Kotan et al. (2016)

Electrochemical analysis

The reductive properties of curcumin are due to its ability to rather easily donate electrons; therefore, curcumin can be determined by electrochemical methods. The electrochemical analytical technique has the advantages of simplicity and high sensitivity. However, the major drawback of this method is lack of inherent specificity. Therefore, development of proper separation systems can overcome the above said obstacle. Wray et al. (2012) successfully separated curcumin by chelating it with nickel (II) using the molecular functionality of diketone which contributed for its chelation with nickel (II). Through acidification of the precipitate, recovery of the curcumin from the nickel, the complex is achieved simply and quantitatively. Li et al. (2014c) designed a sensitive graphene-modified glassy carbon electrode for determination of low levels of curcumin. The currents measured in this method presented a good linear relationship with curcumin concentrations in the range of 5.0×10^{-8} to 3.0×10^{-6} mol/L, with a low detection limit of 3.0×10^{-8} mol/L. They also did a sensitivity test by spiking various possible interferences and proved that the proposed method had a reasonable selectivity. Dey et al. (2018) fabricated graphene oxide electrode and reduced graphene oxide modified on glassy carbon electrode respectively. The reported limit of detection using this sensor is 0.9 pM/mL which is the lowest to date for any plant-based component using any bio sensor method. However, these methods can only determine the concentration of curcumin only. The major limitation of these methods is that reported information is not available about other curcuminoids content. Comparison of different analytical methods based on detection limit of curcumin was given in Table 4.

Conclusion

Many research reports on turmeric have revealed that its bioactive compounds called curcuminoids have an exceptionally wide range of beneficial health properties. Due to these properties, many foods, pharmaceutical, and cosmetic industries are using curcuminoids as an ingredient in food formulations. Therefore, monitoring these bioactive components during processing and storage is critical for its quality control in turmeric powder and processed products.

- Spectrophotometric is the simple method for curcumin estimation, but it is useful only when individual curcuminoids concentration is not an important quality parameter.
- Infrared spectrometry method is rapid, nondestructive and best suits for quality control in industries.
- Separation of curcuminoids with TLC method before quantification allows identification of low levels on curcuminoids without any interference with other compounds. However, mobile phase optimization, the broadness of spots, plate-to-plate variation, is major limitations for TLC and HPTLC methods.
- The highest number of reports is available for estimation of curcuminoids using HPLC. Nevertheless, these methods are highly dependent on sample matrix type.
- For determining very low levels of curcuminoids in any sample matrices, LC–MS/MS is the best choice.
- Spectrofluorimetry and Electrochemical methods have been gaining attention because of their advantages. However, like the spectrophotometric method, these methods cannot give the relative composition of each curcuminoids.

Overall, researchers are working hard to improve the efficiency of instrumental analytical methods by focusing

on sample preparation procedures, which allows a single analytical method to cover a wide range of sample matrices, and give low levels of detection.

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Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest.

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