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Curcumin: Analysis and Stability

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ABSTRACT

Curcumin is a polyphenol extracted from *Curcuma longa*, used as a spice, in food coloring, and as a traditional herbal medicine. It has wide therapeutic platform as anti-oxidant, anticancer, anti-inflammatory and anti-infection properties. This review discusses the analytical methods used in determination of curcumin in various matrices with degradation profile, expected degradation products and stability tests.

Keywords: *Anti-cancer; Anti-inflammatory; Anti-oxidant; Curcumin analysis; Curcumin degradation; Curcumin stability*

INTRODUCTION

Curcumin, (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dionealso known as diferuloylmethane **Figure 1**, is a phenolic compound[1] present in many kinds of medicinal plants, especially in *Curcuma longa* (turmeric)[2], and was first discovered and isolated in 1815 by Harvard College laboratory scientists *Vogel* and *Pelletier*[3]. The first article referring to the use of Curcumin in human diseases was published in 1937[4].Curcumin possesses many pharmacological activities including antioxidant, anti–infection, anti–inflammation, anti–Alzheimer and anticancer[5–18]. Curcumin is a special spice which is the functional ingredient in curry powder[19], and a potential natural food coloring[20]; it impairs an attractive yellowish-orange color to food, authorized as a food additive by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1974, it's E number is E 100[21]. It is widely used in food applications including dairy products, fat emulsions, confectionery, soups and sauces[22–31]. In this review paper we are highlighting various analytical techniques (focusing on spectrophotometric and chromatographic techniques) used to detect curcumin in different matrices (biofluids, rhizomes, food and different pharmaceutical dosage forms) also with degradation, degradation products and stability indicating methods under different stress conditions. Moreover, this review summarizes in table forms different conditions of each analytical technique. We hope this review will be helpful to all scientists interested in curcumin therapeutic effects and /or applications on food industry.

Table 1. Reported HPTLC methods for curcumin estimation

Ref.	Matrix Sample	Mobile phase	Stationary phase	Densitometric scanning
59	Rhizomes	Chloroform: ethanol: glacial acetic acid (94:5:1 v/v/v)	Silica gel 60 F_{254}	Scanned at 366nm
60	Polyherbal capsule dosage form	n-hexane, ethyl acetate, acetic acid, and methanol (7:2:0.5:0.5, v/v/v)	Silica gel 60 F_{254}	Camag TLC scanner III using absorbance mode at 404 nm.
61	Rhizomes	Chloroform : methanol (97:3 v/v)	Silica gel 60 F_{254}	Camag TLC scanner III using absorbance mode at 254, 366 and 427 nm.
62	Rhizomes	Chloroform: Ethanol: Glacial acetic acid (9.4:0.5:0.1v/v/v)	Silica gel 60 F_{254}	Camag TLC Scanner–III using absorbance mode at 254.
63	Rhizomes	Toluene: ethyl acetate: methanol (18:1:1 v/v/v)	Silica gel 60 F_{254}	Camag TLC scanner –III using absorbance mode at 254 nm.
64	Rhizomes	Chloroform: Methanol (9.5: 0.5 v/v)	Silica gel 60 F_{254}	Camag TLC scanner –III using absorbance mode at 421 nm.
65	Rhizomes	Toluene- chloroform-methanol (5:4:1, v/v/v)	Silica gel 60 F_{254}	Camag TLC scanner –III using absorbance mode at 430 nm
66	Rhizomes	Chloroform: Methanol: Acetic acid; (9.5: 0.5: 0.1v/v/v)	Silica gel 60 F_{254}	Camag TLC scanner III using absorbance mode at 254 and 366 nm.
67	Rhizomes	Chloroform: methanol (48:2, v/v).	Silica gel 60 F_{254}	Scanned at 425 nm.
68	Rhizomes	Chloroform hexane–Methanol (1:1:0.1, v/v/v)	Silica gel 60 F_{254}	Camag TLC scanner- II using absorbance mode at 254 nm.
69	Rhizomes	Chloroform–methanol–formic acid (80:4:0.8, v/v/v) & petroleum ether–ethyl acetate (90:10, v/v)	Silica gel 60 F_{254}	Scanned at 254 and 365 nm
70	pharmaceutical dosage forms	Chloroform: methanol (9.25:0.75 v/v).	Silica gel 60 F_{254}	Scanned at 430 nm.

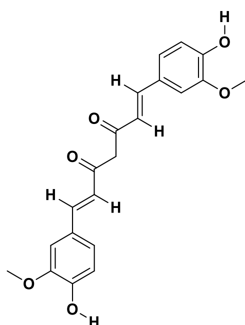

Figure 1. Chemical structure of curcumin

1. Curcumin analysis

1.1 Spectroscopic techniques

1.1.1. Infrared spectroscopy

These techniques had been widely used for determination of curcumin as they allowed rapid and sensitive, ease in sample preparation, and non destructive technique meaning that the used samples can be used for further analysis. In addition, IR spectroscopy could identify and differentiate between curcumin of different geographical origin[32,33],or between curcumin and other Curcuminoids in rhizomes[34,35]. Curcumin had near infrared spectroscopy at regions of 1500-2500 and 2040–2486nm for total Curcuminoids[36–42].

1.1.2. UV-Vis spectrophotometry

Being yellow colored; the most easy and simple method for curcumin estimation is via direct UV-Vis spectrophotometry, as the official standard AOAC method which depends on direct estimation of curcumin content in certain solvents[43], absorption intensity at wavelength of 420 – 430 nm (depending on the solvent system[44]).The absorption band is found to have an asymmetric profile in non-polar solvents (as chloroform, acetic acid, , toluene, and carbon tetrachloride[45]). The type and nature of the solvent affects the absorption profile of curcumin causing only a small red-shift (ca. 0~20 nm) when going from n-hexane to methanol [46] .The PH of solvent also affects the absorption spectrum of curcumin : λ max is 520 nm when measuring curcumin in acetone-bicarbonate buffer (pH 11)[47] ,while in methanol or ethanol solutions

containing 1M HCl λ max is 540 nm [48]. Curcumin may be complexed with cyclodextrin in aqueous solutions

Table 2. Reported HPLC methods for determination of curcumin

Ref	Matrix Sample	Mobile phase	Detection	Column
71	Rhizomes	Methanol : water (75:25 v/v)	UV at 397 nm	RP-C18 column
72	Biofluids (Plasma)	Acetonitrile and triple distilled water (40/60, v/v)	UV at 230 nm	RP-C8 column
73	Pharmaceutical dosage forms	Acetonitrile: ammonium acetate (45:55, v/v, pH 3.5)	UV at 425 nm	RP-C18 column
74	Rhizomes	Acetonitrile and 0.1% formic acid (50:50 v/v)	UV at 425 nm	RP-C18 column
75	Rhizomes and Pharmaceutical dosage forms	(A) 0.1 % formic acid in water & (B) 0.1 % formic acid in acetonitrile	UV at 425 nm	RP-C18 column
76	Rhizomes	Acetonitrile-2% acetic acid (55:45 v/v)	UV at 425 nm	RP-C18 column
77	Pharmaceutical dosage forms	Acetonitrile and water (50:50 v/v) acidified with 2% acetic acid	UV at 425 nm	RP-C18 column
78	Rhizomes	Acetonitrile, methanol and water at 40:20:40 (v/v/v) and pH 3.0	UV at 370nm	RP-C18 column
79	Rhizomes	Aqua bidestilata and acetonitrile (65:35 v/v) containing 1% acetic acid.	UV at 425 nm	RP-C18 column
80	Rhizomes	Acetonitrile–methanol–water (40 : 20 : 40, v/v)	UV at 360 nm	RP-(phenyl) column
81	Rhizomes	Acetonitrile and10 mM Na_2HPO_4–H_3PO_4 (pH 5.0) (50:50,v/v)	Electrochemical detector potential set at 0.9 V.	RP-C18 column
82	Rhizomes	Solvent A (water/acetic acid = 99.9/0.1, v/v) & solvent B (acetonitrile/acetic acid = 99.9/0.1, v/v).	UV at 425 and 254 nm	RP-C18 column
83	Rhizomes	Water and acetonitrile (60/40 vol %).	UV at 425 nm	RP-C18 column
84	pharmaceutical dosage forms	0.1% ortho phosphoric acid and acetonitrile (45:55, v/v)	UV at 262 nm	RP-C18 column
85	Rhizomes	5 mM acetonitrile : phosphoric acid (45:55, v/v)	UV at 425 nm	RP-C18 column
86	Pharmaceutical dosage forms	Ethanol, water and acetonitrile (80:10:10, v/v/v)	Fluorescence detector: Excitation at 365 nm & Emission at 512 nm	RP-C18 column
87	Biofluids (plasma and liver homogenates)	Acetonitrile-methanol-water (pH =3.0)	UV at 425 nm	RP-C18 column
88	Biofluids (plasma)	Acetonitrile-tetrahydrofurane- water containing 0.1% formic acid.	UV at 425 nm	RP-C18 column
89	Rhizomes	Acetonitrile and 0.1% formic acid	UV at 270 and 380 nm	RP-C18 column
90	Biofluids (plasma)	Acetonitrile-methanol-trifluoroacetic acid-water (17.6:35.3:0.1:47.0, v/v/v/v)	UV at 415 nm	RP-C18 column
91	Biofluids (plasma)	Acetonitrile-5% and acetic acid (75:25, v/v)	UV at 420 nm	RP-C18 column
92	Rhizomes	Acetonitrile and 2% v/v acetic acid (40:60, v/v)	UV at 425 nm	RP-C18 column
93	Biofluids (plasma)	Acetonitrile (55%) and citric buffer, pH 3.0 (45%)	UV at 300 and 428 nm	RP-C18 column
94	Rhizomes	Acetonitrile:0.1% trifluro-acetic acid (50:50)	UV at 420 nm	RP-C18 column

Table 3. Reported LC/MS methods for determination of curcumin.

Ref.	Column	Detection	Ionization/ Mass Spectrometry mode	Transitions (m/z)	Mobile phase	Matrix	Internal standard
95	Agilent Poroshell SB-C18 (2.7 µm, 4.6×150 mm)	Thermo TSQ Quantum, SRM	ESI +/MS2 with Quadrupole	369-245-213	0.2 % formic acid and acetonitrile (50:50, v/v)	Plasma	Verapamil
96	Halo C8 (2.7 µm, 4.6 × 50 mm)	AB Sciex Q trap® 6500 MRM	ESI +/MS2 with Triple-Quadrupole	369-177	Acetonitrile-0.2% formic acid in water (73:27 v/v)	Plasma	Dimethyl curcumin
97	Waters Acquity UPLC-BEH-C18 (1.7 µm, 100× 2.1 mm)	AB Sciex Q trap® 5500 MRM	ESI/MS2 with Quadrupole	369-177	Acetonitrile and 0.1% formic acid water with gradient elution	Plasma	Glibenclamide
98	Sepax BRC18 (5 µm, 1.0 ×100 mm)	6490 triple quadrupole MS, MRM	ESI/MS2 with Quadrupole	369-285	Acetonitrile and 0.1% formic acid in water (50:50, v/v)	Plasma	Salbutamol
99	Agilent Zorbax Eclipse XDB C18 (3.5 µm, 4.6 × 50 mm)	Thermo Finnigan LTQ XL iontrap MS, CRM	ESI/ MS3 with Ion Trap MS	369-245-213	A :0.1% Formic acid in water, B: acetonitrile (25:75 v/v)	Plasma	CUR-d6 (Deuterium Labeled Curcumin)
100	Water XBridge BEH C18 (100 mm ×2.1 mm i.d., 2.5 µm,)	Shimadzu Coupled with QTRAP 4500 system	(ESI -) with quadrupole (MRM)	367.1-134	A: [acetonitrile containing 0.1% (v/v) formic acid] B:[Water containing 0.1% (v/v) formic acid]. (43% A: 57% B)	Plasma	Urolithin B
101	ThermoHypersil-Keystone BetaBasic-8 (2.1 mm×50 mm,5mm)	API-3000 LC/MS/MS	(ESI +) with quadrupole (MRM)	367.4-149.1	50% Acetonitrile with0.1% formic acid	Plasma	Hesperetin
102	BEH C18 (2.1 mm, 100 mm; 1.7mm)	Waters Q-TOF Premier quadrupole	ESI-Q-TOF-MS	367.07-217.06	Acetonitrile: 10 mM ammonium formate: formic acid (90:10:0.05v/v/v),	Brain homogenate	Nimesulide
103	Chromolith rod TM (50 mm, 4.6 mm, 5 mm)	API 4000; LC/MS/MS triple quadrupole system,	ESI equipped with triple quadrupole mass	367-217	Acetonitrile:10mMammoniumacetate buffer (pH 3.5) (80:20, v/v)	Plasma	Nimesulide
104	Discovery1 HS C18, 3 mm, 15cm, 2.1 mm	Agilent LC/ MSD Trap-SL ion trap	positive and negative ESI /MS- quadrupole mass spectrometer	367-217	A:buffer (5mM ammonium formate, 0.1% formic acid, in ddH_2O) B: acetonitrile; gradient (in buffer A)	Herbal extract	Not mentioned
105	Phenomnex Luna, C18 (250m×4.6 mm)	Sciex API 4000 tandem mass	(ESI-) with quadrupole (MRM)	373.2 – 137.1	Acetonitrile/water (70:30, v/v) with 0.005% acetic acid 0.05 ml/l.	Plasma	Salbutamol
106	Zorbax Extend-C18 (150 × 4.6 mm I.D.; 5 m)	Micromass Quattro Ultima tandem quadrupole	(ESI-) with quadrupole (MRM)	367 - 217	70% Acetonitrile and 30% 1 mM formic acid	Plasma and herbal extract	Honokiol

giving λ max = 430 nm[49], while curcumin metal complexes(which have better anti-oxidant therapeutic activity) show a main absorption band at 415–430 nm and compared to curcumin alone[7,50,51]. Further more curcumin may be encapsulated in nanoparticles(for better solubility) as poly(l-lactic acid) nanoparticles giving absorption band at 465 nm[52]. However, using this technique it is not possible to separate and to quantify the curcumin from raw Curcuminoids mixture[52–58].

1.2. Chromatographic-based methods

1.2.1 Thin layer chromatography (TLC) and (HPTLC)

Developed TLC methods could be used as a technique for quality control of *Curcuma* rhizomes. Some of the recent published researches related to the use of TLC coupled with high performance liquid chromatography (HPTLC) for analysis of curcumin are collected in the **Table 1**.

1.2.2. High performance liquid chromatography (HPLC).

HPLC techniques are usually the methods of choice for determination of curcumin, the most common detectors used are UV or PDA (as curcumin has absorbance in the visible range). **Table 2** illustrates recent reported analytical methods of curcumin either in food, pharmaceutical formulations, biological fluids (biofluids) or even alone.

1.2.3. Liquid chromatography coupled with mass spectrometry (LC/MS).

LC/MS can be used to detect even trace amounts of curcumin in biological fluids, food or in other complex matrices and provide fast and accurate analysis as an on-line technique. Moreover, it can be used to differentiate from other Curcuminoids. Furthermore it can be used not only to identify and quantify known Curcuminoids, but also to identify unknown Curcuminoids in extracts from turmeric or related plant material. Recent LC/MS methods and their conditions are listed in **Table 3**.

2. Curcumin Degradation

2.1. Oxidation of curcumin

The major product of the autoxidation of curcumin is a bicyclopentadione, formed by oxygenation and double cyclization of the heptadienedione chain connecting the two methoxyphenol rings of curcumin.[107,108]

Products of curcumin oxidative transformation are eight compounds (Bicyclopentadione, Dihydroxy cyclopentadione, Hemiacetal cyclopentadione, Ketohydroxy cyclopentadione, Spiroepoxide cyclopentadione, Vinylether cyclopentadione, Cyclobutyl cyclopentadione and Diguaiacol).[109] Six of these products had oxygen substitutions at C-1 and C-7. Two products that did not incorporate oxygen were a cyclobutyl cyclopentadione and, an obvious cleavage product. Two of the isolated products, the Spiroepoxide and the vinyl ether cyclopentadiones, were intermediates in the reaction to the Bicyclopentadione. The others were end products formed in addition to the Bicyclopentadione.[110] Neither vanillin nor ferulic acid was formed in sufficient amount to be detected.[111]

2.2. Degradation of curcumin in buffered solutions

Decomposition was pH dependent and occurs faster at neutral-basic conditions. The stability was proven to be more in acidic pH and decrease as the pH increases. It was more stable at pH of 1.2; less than 1% of curcumin decomposed within 6hrs of the total curcumin in the absence of light.[112,113]

When curcumin was incubated in phosphate buffer, pH 7.2 at 37˚C(biological media), it was found that 90% was degraded in 30 min. Trans-6-(4-hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexenal, vanillin, ferulic acid and feruloyl methane were identified as degradation products.[114,115]

Curcumin exhibits a red color at pH less than 1, curcumin (due to the presence of the protonated form), and a yellow color at pH ranging from 1 to 7 (as the majority of the curcumin molecules present in the neutral form), while at pH values higher than 7.5 a distinct dark red color rapidly appeared which fade rapidly with time leaving an yellowish orange solution. Furthermore, for the buffer system being used, curcumin forms complexes with borate, citrate, and phthalate, while being inert towards KCl, KH_2PO_4, and $NaHCO_3$[116].

2.3. Photo degradation of curcumin

Exposure to visible light inflicts more degradation than UV light .The photochemical degradation of solid state curcumin exposed to sunlight for 120 h yielded vanillin (34 %), ferulic aldehyde (0.5 %), ferulic acid (0.5 %), vanillic acid (0.5 %) ,p-hydroxybenzaldehyde, *p*-hydroxybenzoic acid [117,118]. Curcumin was found to be more stable in the dried form against sunlight exposure than in solution[119]

Besides the photo-sensitivity of curcumin, it is also self-degradable in the dark, this self-degradation process is enhanced in basic medium, and it was found that this process was fairly dependent on salt (NaCl) concentration.[120]

2.4. Thermal degradation of curcumin

Curcumin is heat sensitive (however it is stable up to 70 °C[121]), current researches suggest that curcumin undergoes thermal degradation due to

Table4. Expected degradation product/s of curcumin for each degradation type

Stress conditions	Degradation products	Ref
Oxidation	Eight compounds: Bicyclopentadione, Dihydroxy cyclopentadione,Hemiacetal cyclopentadione, Ketohydroxy cyclopentadione, Spiroepoxide cyclopentadione, Vinylether cyclopentadione, Cyclobutyl cyclopentadione and Diguaiacol	110
Buffered solutions	Trans-6-(4-hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexenal, vanillin, ferulic acid and feruloyl methane	125 126
Photo-degradation	Vanillin (34 %), ferulic aldehyde (0.5 %), ferulic acid (0.5 %), vanillic acid (0.5 %), *p*-hydroxybenzaldehyde , p-hydroxybenzoic acid	117
Thermal degradation	Vanillin, ferulic acid, and 4-vinyl guaiacol.	122 123

Table 5.The recent reported HPLC methods to assay curcumin degradation

Ref	Column	Mobile phase	Detection	Degradation conditions
127	C18 column. (at 30 °C)	A: 0.05 M KH_2PO_4 adjusted at pH 2.3. B: Methanol. C: Acetonitrile.	FDA at 288 nm	Acidic, alkaline and neutral hydrolysis, photo-degradation, Oxidative degradation and dry heat.
128	C18 column	acetonitrile and 10 mM ammonium acetate buffer (pH adjusted to 3.5)	Tandem mass detector with ESI $^-$	hydrolysis (acidic and alkaline), oxidation, photolysis, and thermal stress
129	C18 column	A :acetonitrile B :Phosphate buffer pH 3, at the ratio of 70:30, 60:40, 55:45, 50:50 and 45:55	PDA At 422 nm	Acid, base, neutral, oxidative, photo and thermal degradation.
130	C18 column	A :(acetonitrile /water 5:95 v/v) B:acetonitrile	(ESI–MS). The scan range was 140–415 m/z	Buffer degradation
112	C18 column	Toluene, Chloroform, and methanol in the ratio of 4:4:2 v/v	UV at 428 nm	Different buffer solutions of pH 1, 1.2, 6.8, 7, and 7.4. in the presence and absence of light

roasting (heating at 180 °C up to 70 minutes) and its degradation products are vanillin, ferulic acid, and 4-vinyl guaiacol.[122] If curcumin was used as food coloring agent, the processing temperature of the food should not exceed 190 °C.[123] Around 27-53 % of curcumin was lost by heat processing of turmeric and major loss was observed by pressure cooking, with maximum loss in pressure cooking for 10 min.[124]

Conflict of Interest

The authors declare that they don't have any kind of interest.

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