

Advances in Chemical Constituents and Quality Control of Turmeric

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Abstract

Turmeric, derived from the rhizomes of *Curcuma longa* L. (Zingiberaceae), is one of the most popular herbal medicines. Its main bioactive constituents include curcuminoids, sesquiterpenes, and terpenoids. It exhibits antitumor, anti-inflammatory, antioxidant, antibacterial, and antiviral activities. With the rapid development of analytical technologies, remarkable progress has been made in studies of turmeric. This review article summarizes research advances in chemical analysis and quality control of turmeric from 2009 to 2018.

Keywords: Bioactive constituents, quality control, review, turmeric

INTRODUCTION

Turmeric, derived from the rhizomes of *Curcuma longa* L. (Zingiberaceae family), has been used as an important herbal medicine in China for >1000 years.^[1,2] According to the traditional Chinese medicine theory, turmeric could promote “qi” and “blood” circulation, remove stagnation, and alleviate ache in human. Modern pharmacological studies indicate that turmeric exhibits diverse biological activities, including antitumor, anti-inflammatory, antioxidant, antimicrobial, and antiviral activities.^[3] Meanwhile, phytochemistry studies reveal that turmeric mainly contains curcuminoids, sesquiterpenes, and terpenoids. As the main bioactive component in turmeric, curcumin (CUR) shows diverse pharmacological activities and has been selected as the chemical marker for quality control of turmeric in the Pharmacopoeia of the People's Republic of China (2015 Edition).^[1] With a characteristic deep orange-yellow color, turmeric is an important ingredient in curry and is widely used as dye, flavor, and cosmetic agents. To meet the market demands, turmeric is extensively cultivated in Guangxi, Yunnan, and Fujian provinces of China though the authentic habitat is Sichuan province.^[2]

Several review articles are available on turmeric.^[3-6] For example, new research progress of turmeric in chemical constituents, biological activities, and *in vivo* metabolism were summarized in 2013 by Li *et al.*^[3] In 2010, our group

also summarized chemical analysis of turmeric.^[5] Herein, we comprehensively summarized English and Chinese literature on chemical constituents and quality control of turmeric published during 2009–2018 from such databases as Web of Science, PubMed, and CNKI (Chinese).

CHEMICAL CONSTITUENTS

Curcuminoids

Curcuminoids are the main components in turmeric. Up to now, >20 curcuminoids have been isolated and identified from turmeric. Among them, CUR, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) are the predominant ones. In addition, hydrogenated and cyclized curcuminoids, such as (4Z,6E)-(+)-1,5-dihydroxy-1,7-bis-(4-hydroxyphenyl)-4,6-heptadien-3-one and curcupalongin A, have been reported recently.^[7] The structures of newly isolated curcuminoids are shown in Figure 1.

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Curcuminoids possess antitumor, anti-inflammatory, and antioxidant activities. Particularly, CUR has been reported to show significant therapeutic effects in treating hepatitis B and alcoholic liver disease.^[8] Moreover, it could also improve memory and cognitive abilities in patients with Alzheimer's disease, due to its anti-inflammatory and anti-amyloid brain effects.^[9]

Sesquiterpenoids

Phytochemical researches have revealed about 60 sesquiterpenoids (most of them belong to bisabolane type) in turmeric, including ar-turmerone, curcumene, β -selinene, α -turmerone, β -turmerone, turmeronol A, bisacurone, 4,5-dihydroxybisabola-2,10-diene, and dehydrozingerone.^[5] In recent years, >10 sesquiterpenoids have been isolated from turmeric, such as longpene C, longpene D, intermedin B, and so on. Their structures are summarized in Figure 2. These sesquiterpenoids possess anti-inflammatory, anticancerous, antiproliferative, and hypocholesterolemic activities.^[10-13]

Terpecurcuminoids

Recently, our group discovered a new type of minor compounds from turmeric which were named as terpecurcuminoids.^[14-16] Their structures are conjugates of curcuminoids with monoterpenes or sesquiterpenes. Thus far, at least 29 terpecurcuminoids

have been reported [structures shown in Figure 3].^[14-17] Among them, 15 derivatives were curcuminoids conjugated with sesquiterpenes through C-C bond, 12 were conjugated through C-O bond, and 2 were conjugated with menthane monoterpene. Some of these terpecurcuminoids showed more potent cytotoxic activities than CUR against different human cancer cell lines (A549, HepG2, MDA-MB-231, and MCF-7). For example, terpecurcumin Q exhibited half maximal inhibitory concentration (IC_{50}) of 3.9 μ M against MCF-7 human breast cancer cells, whereas the IC_{50} of CUR was 31.3 μ M. Further study indicated that terpecurcuminoids could regulate mitochondria-mediated apoptosis, which plays an important role in the overall growth inhibition.^[16-18]

QUALITY CONTROL OF TURMERIC

As the major bioactive chemical components, curcuminoids and sesquiterpenoids are usually used as chemical markers for the quality control of turmeric. Different techniques have been used for qualitative and quantitative analyses, including high-performance thin-layer chromatography (HPTLC), high-performance liquid chromatography (HPLC), HPLC-mass spectrometry (HPLC-MS), gas chromatography (GC), GC-MS, and capillary electrophoresis (CE).

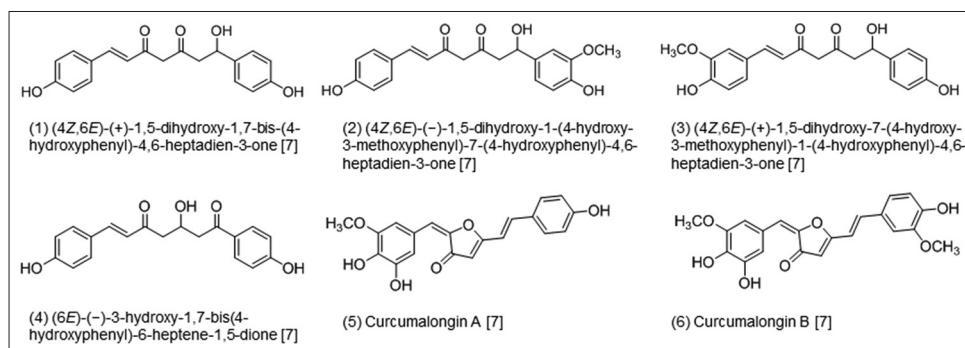


Figure 1: The structures of newly isolated curcuminoids from turmeric

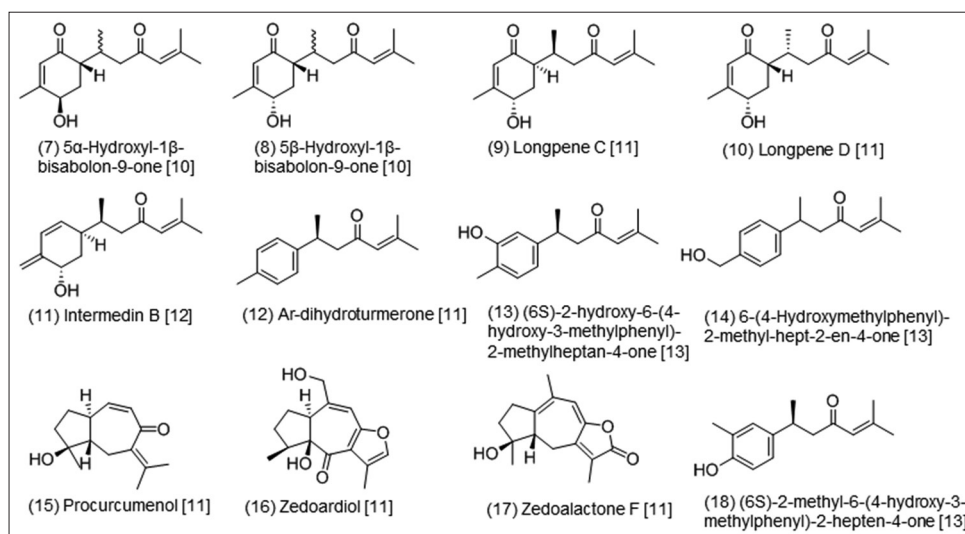


Figure 2: The structures of newly isolated sesquiterpenoids from turmeric

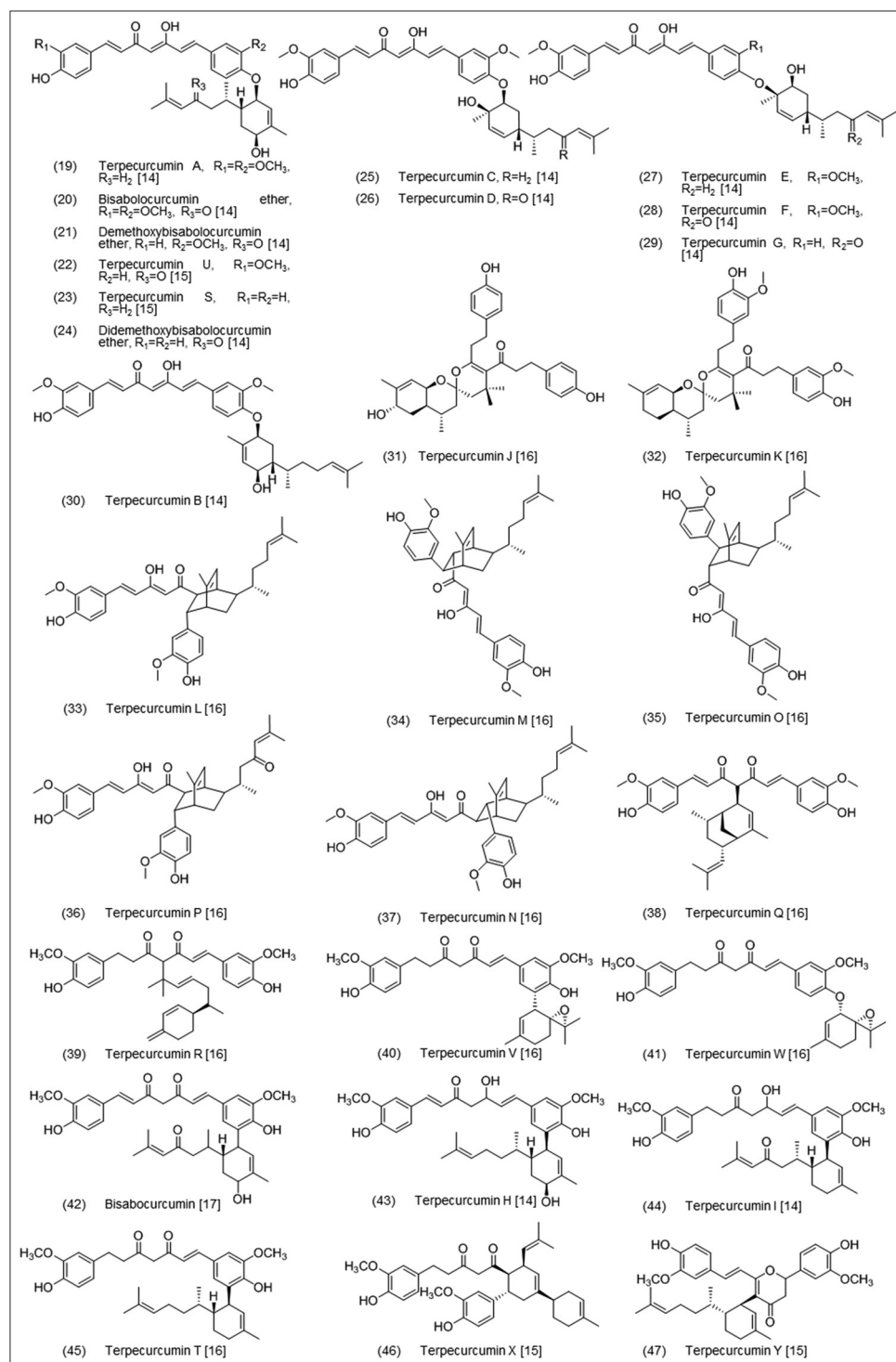


Figure 3: The structures of terpecurcuminoids from turmeric

Qualitative analysis of turmeric

Liquid chromatography-mass spectrometry

Jin *et al.* developed two LC-MS/MS platforms to profile curcuminoids in turmeric. The first step was qualitative analysis in turmeric extract using LC-Quadrupole-Trap-MS/MS based on the MS/MS fragmentation patterns of ten standards. Fifty-three curcuminoids were identified preliminarily.

According to the results, six types of phenyl substitutes and 14 types of heptane skeletons were classified, and potential low-abundant curcuminoids were predicted based on the known substitutes and skeletons. Furthermore, a more sensitive targeted qualitative analysis of curcuminoids was employed using LC-Quadrupole-Time of flight-multiple reaction monitoring (MRM)-enhanced product ion scan mode based on the predicted precursor ions and productions, and 46 trace

curcuminoids were identified.^[19] Recently, our group proposed a novel LC-MS based strategy to globally characterize the chemical constituents in turmeric. This strategy used multiple neutral loss/precursor ion scanning combined with substructure recognition and statistical analysis. As a result, a total of 846 terpecurcumins were discovered, and two unprecedented novel compounds (terpecurcumins X and Y) were purified.^[15]

Gas chromatography-mass spectrometry

GC-MS was widely used for the analysis of essential oil of turmeric. Hu *et al.* established the chemical fingerprints of turmeric by analyzing samples collected from 24 different geographical origins in China by GC-MS, and 46 volatile compounds were characterized. Based on statistical analysis, all the samples could be grouped according to their origins, and turmerone, ar-turmerone, and zingiberene were the characteristic components discriminating these samples.^[20] The result revealed that GC-MS coupled with chemometric techniques could provide a reliable quality control for turmeric. Naz *et al.* analyzed the volatile oil of turmeric by GC-MS, and the chromatographic analysis showed 16 constituents. According to peak areas, the major components were aromatic turmerone (25.3%), α -turmerone (18.3%), curlone (12.5%), caryophyllene (2.26%), and eucalyptol (1.60%).^[21]

Quantitative analysis of turmeric

High-performance thin-layer chromatography

Paramasivam *et al.* developed an HPTLC method to determine curcuminoids on silica gel 60GF₂₅₄ plate with chloroform: methanol (48:2, v/v) as the developing solvent. CUR, DMC, and BDMC showed good separations with this system, with R_f values of 0.66 ± 0.02 , 0.48 ± 0.02 , and 0.30 ± 0.02 , respectively. The calibration plot of peak area versus concentration was linear with correlation coefficient (r) higher than 0.9998.^[22] Zhang *et al.* developed a qualitative and quantitative method to analyze eight curcuminoids and sesquiterpenoids in four species of *Curcuma*, including *C. phaeocaulis*, *C. kwangsiensis*, *C. wenyujin*, and *C. longa*. The analysis was performed on silica gel 60F₂₅₄ plates with chloroform-methanol-formic acid (80:4:0.8, v/v/v) as the developing solvent for the first separation and petroleum ether-ethyl acetate (90:10, v/v) for the second separation. The results indicated that turmeric could be easily discriminated from other species of *Curcuma*. CUR, DMC, and BDMC were the major compounds in turmeric, curcumenol was abundant in the rhizomes of *C. phaeocaulis*, and curzerene only existed in *C. wenyujin*.^[23]

High-performance liquid chromatography

The contents of curcuminoids in eight herbal medicines derived from four *Curcuma* species were determined in our laboratory. The results suggested that CUR, DMC, and BDMC showed good linearity ($r > 0.9998$) in the concentration ranges of 4.88–625, 4.29–550, and 3.98–510 $\mu\text{g/mL}$, respectively. Among the eight samples, turmeric contained the highest amounts of curcuminoids (40.36 mg/g), which were almost 20 times higher than *Huangsi Yujin* (1.94 mg/g)

and 400 times higher than *PengEzhu* (0.098 mg/g).^[24] Avula *et al.* developed an ultra-performance LC coupled with diode array detection method to determine curcuminoids (detected at 420 nm) and ar-turmerone (detected at 240 nm) in different species of *Curcuma* and related dietary supplements. These compounds were successfully separated within 3.5 min on a reversed-phase C18 column at 35°C. The results also revealed that turmeric contained the highest amounts of curcuminoids and ar-turmerone.^[25]

The contents of bioactive components in turmeric could be affected by environmental conditions. Chao *et al.* used HPLC method to determine CUR, DMC, BDMC, ar-turmerone, α -turmerone, and β -turmerone in 14 batches of turmeric samples from different regions. The results revealed that the contents of curcuminoids in all samples meet the requirement of the Pharmacopoeia of the People's Republic of China though the volatile compounds (ar-turmerone, α -turmerone, and β -turmerone) varied remarkably due to different cultivating sites and harvest times.^[26] Our group also found that samples from Sichuan province contained remarkably higher amounts of curcuminoids (22.21–40.36 mg/g) than those from other cultivation regions. HPLC with different detectors or columns were used in the quality control of turmeric. Long *et al.* developed an HPLC coupled with electrochemical detection method to determine three curcuminoids in turmeric, which showed good linearity and high sensitivity (limit of detection [LOD] reached up to 10^{-8} M).^[27] Osorio-Tobón *et al.* used fused core column to analyze CUR, DMC, and BDMC in turmeric, which showed good chromatographic performances, and the separation was achieved within only 1.3 min [Figure 4].^[28] Detailed parameters of these methods were summarized in Table 1.

Liquid chromatography-mass spectrometry

Shen *et al.* developed an LC/MS/MS method to simultaneously identify and quantify CUR, DMC, and BDMC in turmeric. Using the MRM scan mode, Limit of Quantity for CUR, DMC, and BDMC was 0.08, 0.53, and 0.05 ng/mL, respectively.^[29] Ashraf *et al.* used an ultra-HPLC-tandem MS ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) to determine the contents of three major curcuminoids in turmeric from India. The contents of CUR, DMC, and BDMC in turmeric from different geographical regions varied remarkably.^[30]

Capillary electrophoresis

Anubala *et al.* developed a nonaqueous CE method to determine CUR, DMC, and BDMC in turmeric. The three compounds showed good linearity ($r^2 > 0.998$), reproducibility (relative standard deviation $< 2.5\%$), and sensitivity (LOD $< 14.6 \mu\text{g/mL}$).^[31,32] Li *et al.* used microemulsion electrokinetic chromatography with an ionic liquid as the oil phase to determine the contents of CUR, DMC, and BDMC. The separation was achieved within 9 min in a 100-mM sodium dodecyl sulfate, 1.6-M n-butanol, and 20-mM[BMIM]PF₆ in 10-mM borate buffer at pH 10.2.^[33]

Table 1: High-performance liquid chromatography methods for the analysis of curcuminoids and sesquiterpenes in turmeric samples

| Analytes | Stationary phase | Mobile phase | Detector | Linearity range (µg/mL) | Correlation coefficient | LOD | References |
|--|--|--|---|--|-------------------------|--|------------|
| CUR DMC BDMC | YMC ODS-A C18 column (250 mm × 4.6 mm, 5 µm) | CH ₃ CN-0.1% formic acid-water | DAD-270 nm | 4.88-625 4.29-550 3.98-510 | $r^2 > 0.9998$ | 18.9 ng/mL 16.7 ng/mL 15.4 ng/mL | [24] |
| CUR DMC BDMC ar-turmerone | Acquity UPLC BEH Shield RP18 Column (50 mm × 2.1 mm, 1.7 µm) | 0.05% formic acid-CH ₃ CN-0.05% formic acid-water | DAD-420 nm for curcuminoids; 240 nm for sesquiterpenes | 1-25 0.03-25 0.03-25 0.1-25 | $r^2 > 0.9991$ | 30 ng/mL 30 ng/mL 30 ng/mL 100 ng/mL | [25] |
| CUR DMC BDMC ar-turmerone β-turmerone α-turmerone | Zorbax SB-C18 column (250 mm × 4.6 mm, 5 µm) | CH ₃ CN-0.4% acetic acid-water | DAD-420 nm for curcuminoids; 240 nm for sesquiterpenes | 1.56-100 1.56-100 3.13-100 6.25-400 3.13-200 3.13-200 | $r^2 \geq 0.9999$ | 1.04 µg/mL 0.88 µg/mL 0.67 µg/mL 2.45 µg/mL 1.71 µg/mL 3.02 µg/mL | [26] |
| CUR DMC BDMC | Wondasil C18 column (250 mm × 4.6 mm, 5 µm) | CH ₃ CN-10 mM Na ₂ HPO ₄ -H ₃ PO ₄ (pH 3.0) | ECD | 0.077-15.314 0.066-13.321 0.070-35.123 | $r^2 > 0.9985$ | - | [27] |
| CUR DMC BDMC | Fused-core C18 column (100 mm × 4.6 mm, 2.6 µm) | 0.1% acetic acid-CH ₃ CN-0.1% acetic acid-water | DAD-425 nm | 0.5-100 0.1-75 0.25-75 | $r^2 \geq 0.9999$ | 1.34 ppm 0.67 ppm 0.64 ppm | [28] |

LOD: Limit of detection, CUR: Curcumin, DMC: Demethoxycurcumin, BDMC: Bisdemethoxycurcumin, DAD: Diode array detection, UPLC: Ultra-performance liquid chromatography, ECD: Electrochemical detection, YMC ODS: YMC octadecyl silane, BEH: Ethylene bridged hybrid

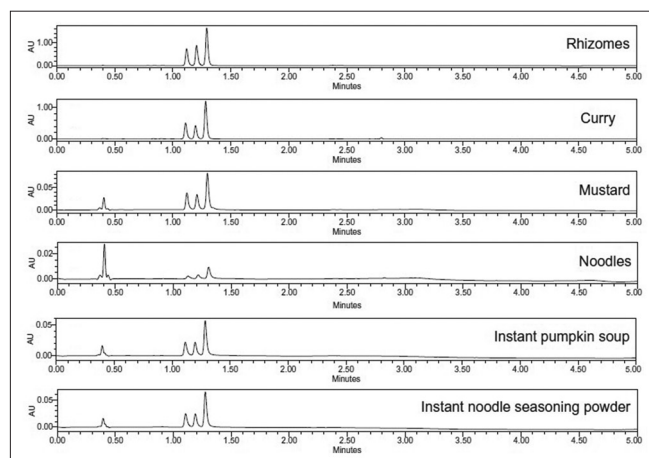


Figure 4: Representative high-performance liquid chromatography chromatograms of different types of turmeric samples. A: Turmeric rhizomes, B: Curry, C: Mustard, D: Noodles, E: Instant pumpkin soup, F: Instant noodle seasoning powder^[28]

Heavy metals

Chen *et al.* developed an inductively coupled plasma-MS method to determine inorganic elements in turmeric from Guangxi province. The contents of Pb, Cr, Cd, and Cu in turmeric were 1.59, 0.76, 3.39, and 23.4 µg/g, respectively.^[34] Chen *et al.* used graphite furnace atomic absorption spectrometry and atomic fluorescence spectrometry to determine Cu, Pb, Cd, Cr, As, and Hg in turmeric, respectively. The results revealed that 36.4%, 18.2%, and 9.1% of the samples did not meet the requirements for Cr, Cu, and Pb, respectively.^[35]

CONCLUSION

The quality control of turmeric is mainly focused on curcuminoids and sesquiterpenoids. Particularly, CUR, DMC, and BDMC are widely used as chemical markers, and they are mainly analyzed by HPLC or LC-MS. GC and GC-MS are used for the analysis of sesquiterpenoids. With the development of techniques in recent years, the sample could be analyzed within a few minutes. In the future, it is necessary to establish new methods monitoring curcuminoids, sesquiterpenoids, heavy metals, and even pesticides in turmeric. The methods could be used to test at least tens of batches of representative samples collected from different locations to establish high-level quality standards.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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