Short Communication

The stability and degradation products of polyhydroxy flavonols in boiling water

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ABSTRACT

Polyhydroxy flavonols readily degraded during thermal processing. In this study, the UPLC-Q-tof-MS/MS was applied to explore the stability of dietary polyhydroxy flavonols, myricetin, kaempferol, galangin, fisetin, myricitrin, quercitrin and rutin, in boiling water. The decomposition of flavonols was mainly caused by the heterocyclic ring C opening to form simpler aromatic compounds. The degradation products mainly included 1,3,5-benzenetriol, 3,4,5-trihydroxybenzoic acid, 2,4,6-trihydroxybenzoic acid and 2,4,6-trihydroxybenzaldehyde, etc. Compared with myricetin with a pyrogallol-type structure on the ring B, the glycoside in myricitrin slightly affects the stability. However, the glycosides in rutin and quercitrin dramatically improved the stability in water. During the boiling process, flavonols underwent a series of chemical reactions, such as hydroxylation, dehydroxylation, deglycosidation, deprotonation, and C-ring cleavage.

1. Introduction

Over the last few decades, the epidemiological and nutritional data have shown that consuming vegetables and fruits rich in flavonoids leads to a general well-being of consumers (Liu, Fu, Ma, Yi & Cai, 2021; Higbee et al., 2022; Ozdal et al., 2016; Xiao, 2017; Xiao et al., 2016; Yang et al., 2022; Zhang et al., 2021; Zhao et al., 2020). It is mainly attributed to various dietary bioactive flavonoids, which showed numerous functions such as free radical scavenging (Rodriguez-Mateos et al., 2014), anti-inflammatory (Chen et al., 2018), anti-cancer (Kim et al., 2019), hypoglycemic (Bolouki, Zal & Bordbar, 2020; Kim et al., 2019) and weight loss (Lyu et al., 2022), etc., which played a crucial role in promoting health (Dong et al., 2021; Zhong et al., 2022). However, the bioactivities of dietary flavonoids depend largely on their stability in the food matrix (Xiao and Högger, 2015; Cao et al., 2016; Zhang et al., 2022; Chandra, Prihastyanti & Lukitasari, 2021).

There have been a lot of studies on the effects of thermal treatment on flavonoids (Ganesan, Sukalingam & Xu, 2019; Hidalgo and Zamora, 2017; Wong, Chai & xiao, 2019; Chandra et al., 2021); however, the thermal degradation products and mechanisms of polyhydroxy flavonols in boiling water are still not clear. Herein, we selected the stability of seven polyhydroxy flavonols (Fig. 1) in boiling water were investigated for simulating common home cooking conditions via UPLC-Q-tof-MS-MS analysis.

We further identified the thermal degradation products structures and revealed their thermal degradation mechanisms. The flow diagram is shown in Fig. 2.

2. Materials and methods

2.1. Chemicals

Myricetin, kaempferol, galangin, fisetin, myricitrin, quercitrin and rutin (>95%) were purchased from Yuanye Biotechnology Co. Ltd. (Shanghai, China). Methanol (LC-MS grade) was purchased from Merck Co. Ltd. (Darmstadt, Germany). Formic acid (HPLC grade) and DMSO were obtained from Aladdin Co. Ltd. (Shanghai, China). Deionized water was prepared using a MilliQ Integral water purification system (Millipore, Bedford, MA, USA).

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E-mail addresses: linshiye33@163.com (S. Lin), jsimal@uvigo.es (J. Simal-Gandara), hui_cao0830@yahoo.com, mprieto@uvigo.es (H. Cao), jianboxiao@yahoo.com (J. Xiao).
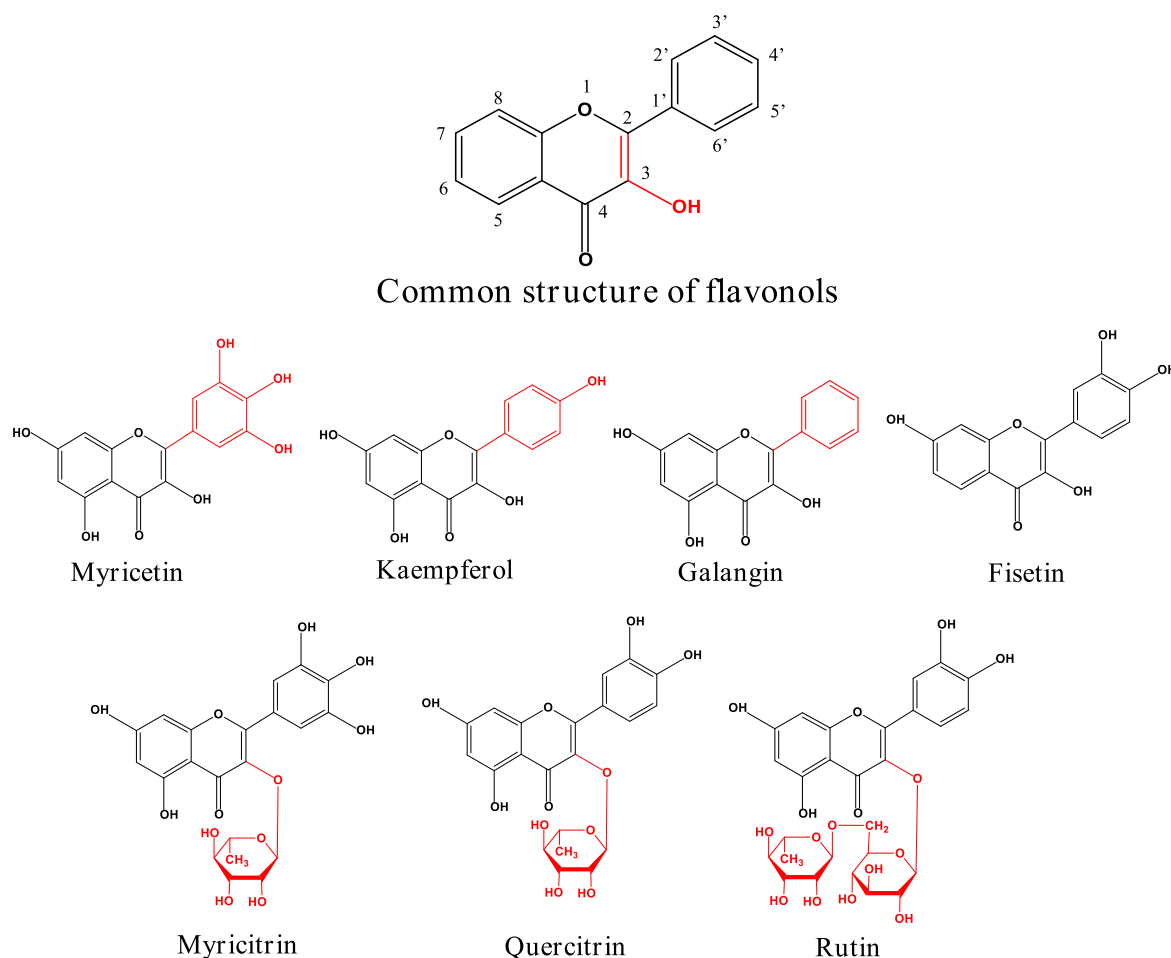
Fig. 1. Chemical structures of flavonols studied.

2.2. Stability of flavonols in boiling water

Flavonol was dissolved in DMSO to obtain a standard stock solution (5×10^{-3} mol/L). One hundred microliters of flavonol standard stock solution were added to 900 μL MiliQ water in an autosampler vial. The vial was incubated in a boiling water bath, and the sample was taken out from the vial every 15 min, and was immediately cooled in an ice bath for further UPLC-Q-tof-MS/MS analysis.

2.3. UPLC-Q-tof-MS analysis

UPLC-Q-tof-MS/MS analysis was performed on an ultra-performance liquid chromatography system coupled to the time-of-flight mass spectrometry (Waters XEVO G2-XS QTof). Chromatographic separation on the system was achieved on a Waters ACQUITY UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm). The mobile phase was a gradient of 0.1% formic acid in MiliQ water (A) and methanol (B) at a flow rate of 0.3 mL/min. The injection volume was 1 μL. The elution gradient was set as follows: 5–15% B, 0–2 min; 15–25% B, 3–4 min; 25–40% B, 4–5 min; 40–50% B, 5–6 min; 50–60% B, 6–7 min; 60–70% B, 7–8 min; and 70-5% B, 8–13 min. Acquisition range was 100–1000 m/z. Source temperature was 120 °C. Desolvation temperature was 450 °C. Capillary voltage was 2 kV. Sampling cone voltage was 40 V. Source Offset was 80 V. Cone gas flow was 50 L/h. Desolvation gas flow was 700 L/h. MS Data was acquired in MSE mode under sensitivity mode and negative electrospray ionization (ESI-). The data was processed by MassLynx V 4.1 software.

2.4. Strategies for determination of the chemical structures of flavonols derivatives

MS and MS/MS data, fragment ions, chemical reaction properties of flavonols and chemical reaction properties of candidate compounds were combined to infer the chemical structures of the derivatives. Taking myricetin as an example, it was determined whether the derivative contained the characteristic fragment ions of myricetin or myricetin after chemical modification such as oxidation. Secondly, based on the accurate molecular weight provided by MS information and the consideration of likely chemical reactions, the possible chemical structures of the myricetin derivatives were inferred. The structures of the degradation products of the other six flavonols were also predicted according to the above method.

3. Results and discussion

3.1. Stability of polyhydroxy flavonols in boiling water

Fig. 3 and Table 1 showed the stability of myricetin, kaempferol, galangin, fisetin, myricitrin, quercitrin and rutin in boiling water. All these polyhydroxy flavonols were rapidly degraded when heated with in boiling water. The thermal stability in descending order was: galangin > rutin > fisetin > kaempferol > quercitrin > myricitrin > myricetin. Among them, galangin (no hydroxyl group in the B-ring) ($^{500}T_{10} > 180$ min) was the most stable one in boiling water and less than 10% of galangin was degraded after 3 h heating process. The hydroxylation at the ring B of flavonols obviously influenced the thermal stability.
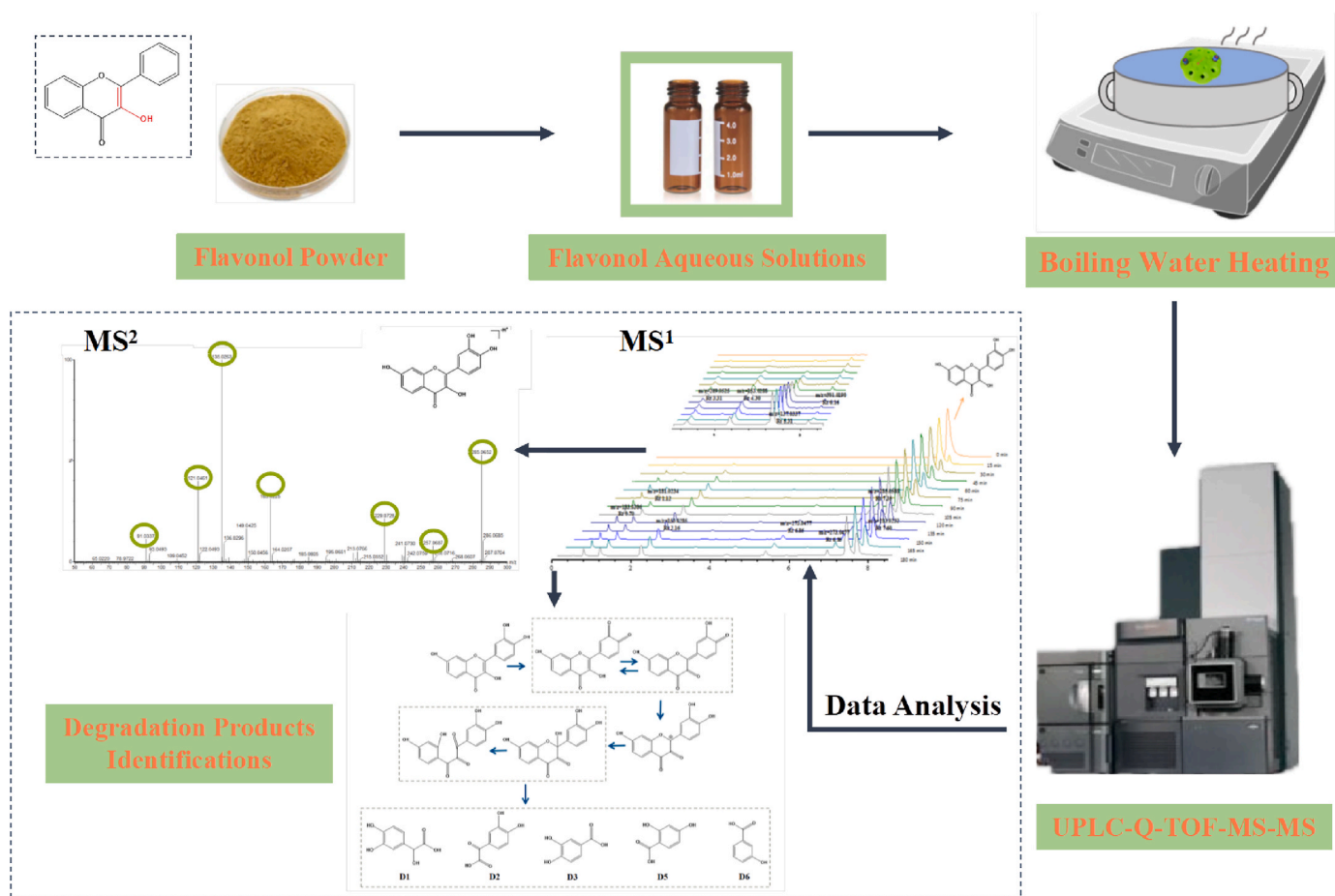
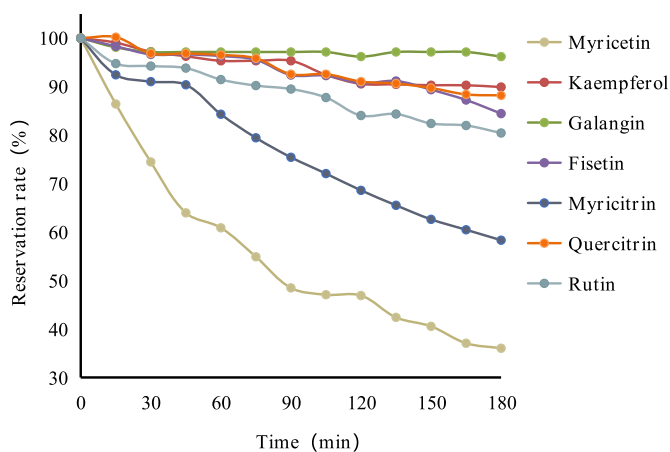**Fig. 2.** Flow diagram demonstrating the stability of flavonols during heating.

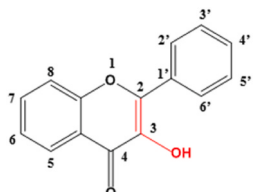**Fig. 3.** Degradation curve of flavonols in aqueous solution at 100 °C.

Myricetin (3′,4′,5′-OH) ($^{500}T_{10} = 7.75$ min) was significantly unstable in boiling water and they were degraded by more than 63.97% of myricetin was disappeared after 3-h heating. Combined with previous experiments on the stability of quercetin (3′,4′-OH) ($^{500}T_{10} = 17.57$ min) in boiling water (Lin et al., 2022), it was shown that B-ring hydroxylation reduces the stability of flavonols and the thermal stability was resorcinol-type > catechol-type > pyrogallol-type. These results were in good agreement with observations of the stability of flavonoids in DMEM medium (Xiao and Högger, 2015). Compared quercetin (3,5,7,3′,4′-OH) and fisetin (3, 7,3′,4′-OH) which both have 2 hydroxyl groups on ring B but different

number of hydroxyl groups on ring A. During heating in boiling water, fisetin ($^{500}T_{10} = 131.24$ min) exhibited higher thermal stability than quercetin ($^{500}T_{10} = 17.57$ min) (Lin et al., 2022), which suggested that the hydroxylation in ring A of flavonols improved its stability. Moreover, the glycosylation on the hydroxyl group of flavonols significantly enhanced their stability. Compared with quercetin ($^{500}T_{10} = 17.57$ min), quercitrin ($^{500}T_{10} = 74.08$ min) and rutin ($^{500}T_{10} = 135.64$ min) showed much higher stability during 3-h heating treatment. Myricitrin ($^{500}T_{10} = 34.43$ min) was also more stable than myricetin ($^{500}T_{10} = 7.75$ min). However, althrough myricitrin has a glycoside on C-3 position, it was still unstable due to the pyrogallol moiety on ring B, which is the key part affecting the stability.

3.2. Identification of new products of myricetin in boiling water

In order to characterize the thermal degradedation products of flavonols in boiling water, the UPLC-Q-tof-MS/MS analysis was applied. The main results were shown in Fig. 4A and Table 2. Myricetin was degraded rapidly in boiling water and formed several new products with peaks at m/z 169.0218 (A1), m/z 169.0214 (A2), m/z 333.0300 (A3), m/z 153.0264 (A4), m/z 301.0041 (unidentified product), m/z 331.0142 (A5) and m/z 343.0146 (unidentified product). Compound A3 was identified as the characteristic degradation product of myricetin, which reached its maximum intensity after 15-min incubation and then gradually decreased. Compound A3 was the hydroxylated product of myricetin, while compound A5 was an o-quinone further deprotonated from A3. The oxidation of flavonols easily opens the heterocyclic ring C, but the introduction of a hydroxyl group from H_2O is not stable and continues to undergo intramolecular rearrangements or tautomerization to forming chalcone and ring B quinones (Zhou et al., 2007). Compared

Table 1

Stability of seven flavonols (initial concentration 500 μM) in boiling water at 100 °C.

Name	Substitutions		500T10	500T50
	OH	others	min	min
Myricetin	3,5,7,3′,4′,5′		7.75	107.24
Kaempferol	3,5,7,4′		101.20	>180
Galangin	3,5,7		>180	>180
Fisetin	3,7,3′,4′		131.24	>180
Myricitrin	5,7,3′,4′,5′	3-O-β-D-glucopyranose	34.43	>180
Quercitrin	5,7,3′,4′	3-O-β-D-glucopyranose	74.08	>180
Rutin	5,7,3′,4′	3-O-α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranose	135.64	>180
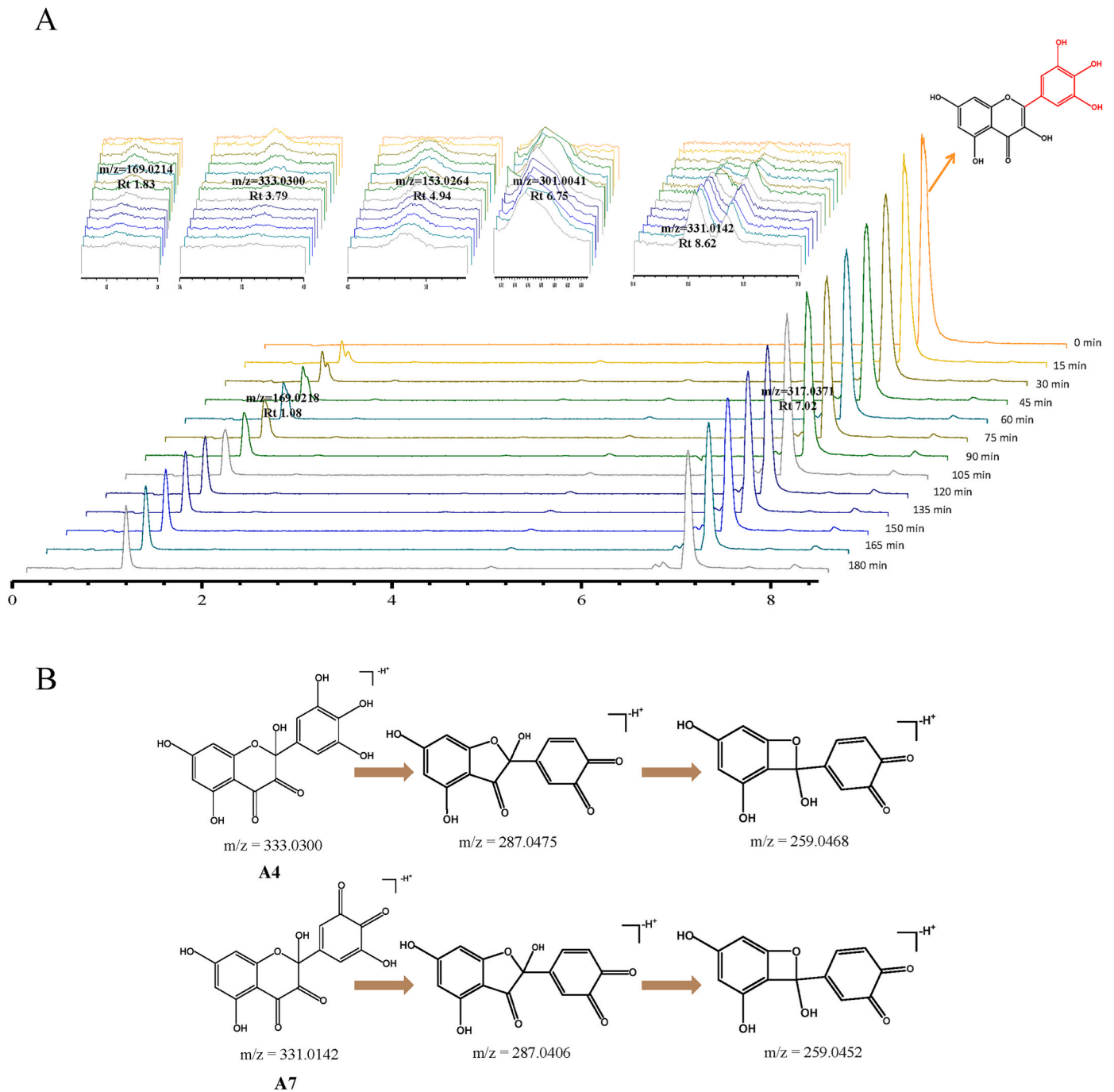
Fig. 4. (A) TIC chromatograms of myricetin in boiling water. (B) Fragmentation scheme of myricetin degradation products.

Table 2

Retention time (R_t), MS-MS fragments of important ions present in the mass spectra of seven flavonols degraded products in boiling water via UPLC-Q-tof-MS.

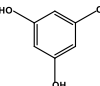| Compounds	Rt (min)	Molecular [M-H]-	MS-MS fragment
Myricetin in 100 °C water			
A1	1.08	169.0218	169.0335, 151.0199, 125.0394, 107.0280, 97.0427
A2	1.83	169.0214	169.0312, 151.0196, 125.0365, 107.0277, 83.0263
A3	3.79	333.0300	287.0475, 259.0468, 253.0421, 207.0115, 125.0385
A4	4.94	153.0264	153.0350, 151.0196, 107.0270
Not identified	6.75	301.0041	301.0213, 273.0239, 245.0290, 229.0335, 201.0374,
Myricetin	7.02	317.0371	317.0535, 289.0568, 271.0453, 227.0546, 193.0314,
Not identified	8.13	343.0146	343.0325, 325.0217, 315.0358, 299.0407, 287.0403, 269.0296, 229.0333, 151.0194
A5	8.62	331.0142	287.0406, 259.0452, 215.0531, 187.0581
Kaempferol in 100 °C water			
B1	0.85	125.0328	97.0553, 83.0464, 77.0204
B2	1.09	169.0222	153.0353, 151.0208, 125.0423, 107.0289, 83.0283
B3	1.79	169.0223	169.0316, 151.0206, 125.0396, 107.0285, 83.0278
B4	3.44	137.0329	111.0259, 93.0484, 75.0389
B5	5.10	153.0275	153.0222, 151.0083, 125.0318
B6	6.61	409.0604	393.0736, 363.0708, 319.0810, 298.0355, 257.0653, 243.0527, 277.0541, 211.0621, 151.0200, 107.0279
B7	6.96	467.0638	449.0705, 405.0871, 377.0896, 337.0966, 297.0615, 285.0610, 269.0682, 253.0714, 181.0209, 137.0403,
Kaempferol	8.33	285.0504	285.0622, 255.0509, 239.0547, 227.0545, 211.0589, 187.0580, 159.0617, 143.0661, 117.0497
Not identified	9.23	569.0735	551.0902, 499.0782, 405.0862, 311.0419, 257.0656, 239.0547, 151.0201
Galangin in 100 °C water			
C1	0.87	125.0322	117.0021, 83.0279, 57.0460
C2	1.09	169.0200	151.0169, 125.0362, 107.0261, 83.0253
C3	1.83	169.0168	169.0279, 151.0172, 125.0372, 107.0266, 83.0258
C4	2.37	121.0372	No data obtained
C5	5.05	153.0269	151.0169, 125.0506, 107.0236
C6	9.21	393.0533	377.0792, 321.0912, 269.0609, 169.0789, 123.0214
Galangin	9.57	269.055	269.0657, 252.0582, 227.0502, 197.0753, 169.0799,
C7	10.29	451.0570	435.0387, 385.0263, 269.0604, 255.0695, 169.0276, 163.0170, 151.0165, 137.0376
Fisetin in 100 °C water			
D1	0.70	183.0386	137.0413, 121.0454, 109.0447, 93.0491
D2	1.12	181.0232	135.0257, 109.0451, 91.0334
D3	2.16	153.0288	153.0326, 109.0424, 91.0208, 81.0466
D4	3.31	269.0526	269.0691, 241.0730, 225.0770, 197.0805, 183.0640
D5	4.30	153.0288	153.0334, 109.0420, 67.0287
D6	5.31	137.0336	137.0412, 135.0259, 109.0449, 91.0339
D7	6.16	301.0190	301.0515, 285.0951, 271.0404, 255.0466, 277.0501, 211.0566, 201.0689, 183.0592, 151.0163
D8	6.85	273.0477	257.0535, 197.0442, 163.0207, 135.0261, 109.0454,
Fisetin	7.35	285.0588	285.0652, 257.0687, 229.0728, 163.0225, 135.0263, 121.0461, 91.0337
D9	7.60	283.0232	283.0491, 255.0527, 277.0566, 211.0607, 182.0646, 171.0639, 147.0265, 135.026, 119.0303, 91.0337
Myricitrin in 100 °C water			
E1	0.88	125.0312	83.0230
E2	1.12	169.0219	151.0188, 107.0223, 83.0281
E3	1.90	169.0221	151.0114, 125.0369, 107.0236, 83.0259
Not identified	3.66	355.0718	355.0827, 309.0769, 153.0246, 83.0295
E4	5.29	469.0733	453.0736, 421.0406, 381.0408, 327.0260, 319.0400, 267.0326, 179.0078, 151.0188, 125.0405
E5	6.04	455.0768	39.0960, 423.0494, 407.0341, 393.0391, 287.0299
Myricitrin	6.70	463.0931	445.0908, 317.0420, 271.0381, 179.0105, 151.0151
Not identified	6.94	509.0780	417.0436, 333.0132, 317.0474, 301.0462, 271.0330,
Not identified	8.18	733.0981	587.0588, 475.1033, 393.0396, 307.0349
Quercitrin in 100 °C water			
F1	5.28	445.0815	445.0968, 415.0592, 299.0359, 221.0310
F2	6.03	445.0823	299.0346, 271.0384, 227.0472, 197.0065
Quercitrin	7.17	447.1078	447.0257, 373.0764, 301.0518, 271.0414, 255.0460,
F3	8.22	453.0981	375.0719, 301.0504, 285.0567, 271.0390, 223.0270
Rutin in 100 °C water			
G1	4.72	607.1331	581.0595, 453.1035, 299.0438, 171.9053
G2	6.13	607.1141	601.0953, 583.0806, 419.0679, 301.0570, 151.0197
G3	6.36	607.1290	607.1645, 315.0381, 301.0576, 287.0422, 151.0198
Rutin	6.71	609.1500	609.1802, 373.0816, 343.0704, 301.0581, 271.0464,
G4	7.13	607.1299	607.1656, 443.0902, 317.0535, 259.0462, 151.0201

with standards, compound A1 (3,4,5-trihydroxybenzoic acid), A2 (2,4,6-trihydroxybenzoic acid) and A4 (2,4,6-trihydroxybenzaldehyde) were also identified (see Table 3). The degradation of myricetin was based on the formation of simpler aromatic compounds by opening heterocyclic ring C. Unfortunately, there were some unidentified compounds, such as m/z 301.0041 and m/z 343.0146.

3.3. Identification of new products of kaempferol in boiling water

As shown in Fig. 5A, and the new products of kaempferol in boiling water included m/z 125.0328 (B1), m/z 169.0222 (B2), m/z 169.0223

(B3), m/z 137.0329 (B4), m/z 153.0275 (B5), m/z 409.0604 (B6), m/z 467.0638 (B7) and m/z 569.0735 (B8). Compared with the standards, compound B1 (1,3,5-benzenetriol), B2 (3,4,5-trihydroxybenzoic acid), B3 (2,4,6-trihydroxybenzoic acid), B4 (4-hydroxybenzoic acid) and B5 (2,4,6-trihydroxybenzaldehyde) were identified. According to the characteristic fragment ions, combined with the chemical properties of kaempferol and the verification of Mass frontier 8.0 software, compound B6 (m/z 409.0604) was speculated that it may contain kaempferol and an phloroglacinol molecule. The presumed structural of compound B6 is shown in Fig. 5B. Compound B7 was found to be kaempferol-3,4-dihydroxymandelic acid. The characteristic fragment ions of

Table 3

Identification of flavonols oxidation products (only simple aromatic compounds are shown).

| Compound	Structure	Myricetin	Kaempferol	Galangin	Fisetin	Myricitrin	Quercitrin	Rutin
1,3,5-Benzenetriol		–	B1	C1	–	E1	–	–
3,4,5-Trihydroxybenzoic acid		A1	B2	C2	–	E2	–	–
2,4,6-Trihydroxybenzoic acid		A2	B3	C3	–	E3	–	–
2,4,6-Trihydroxybenzaldehyde		A3	B5	C5	–	–	–	–
4-Hydroxybenzoic acid		–	B4	–	–	–	–	–
Benzoic acid		–	–	C4	–	–	–	–
3,4-Dihydroxymandelic acid		–	–	–	D1	–	–	–
3,4 -Dihydroxyphenylglyoxylate		–	–	–	D2	–	–	–
Protocatechuic acid		–	–	–	D3	–	–	–
2,4-Dihydroxybenzoic acid		–	–	–	D5	–	–	–
3-Hydroxybenzoic acid		–	–	–	D6	–	–	–
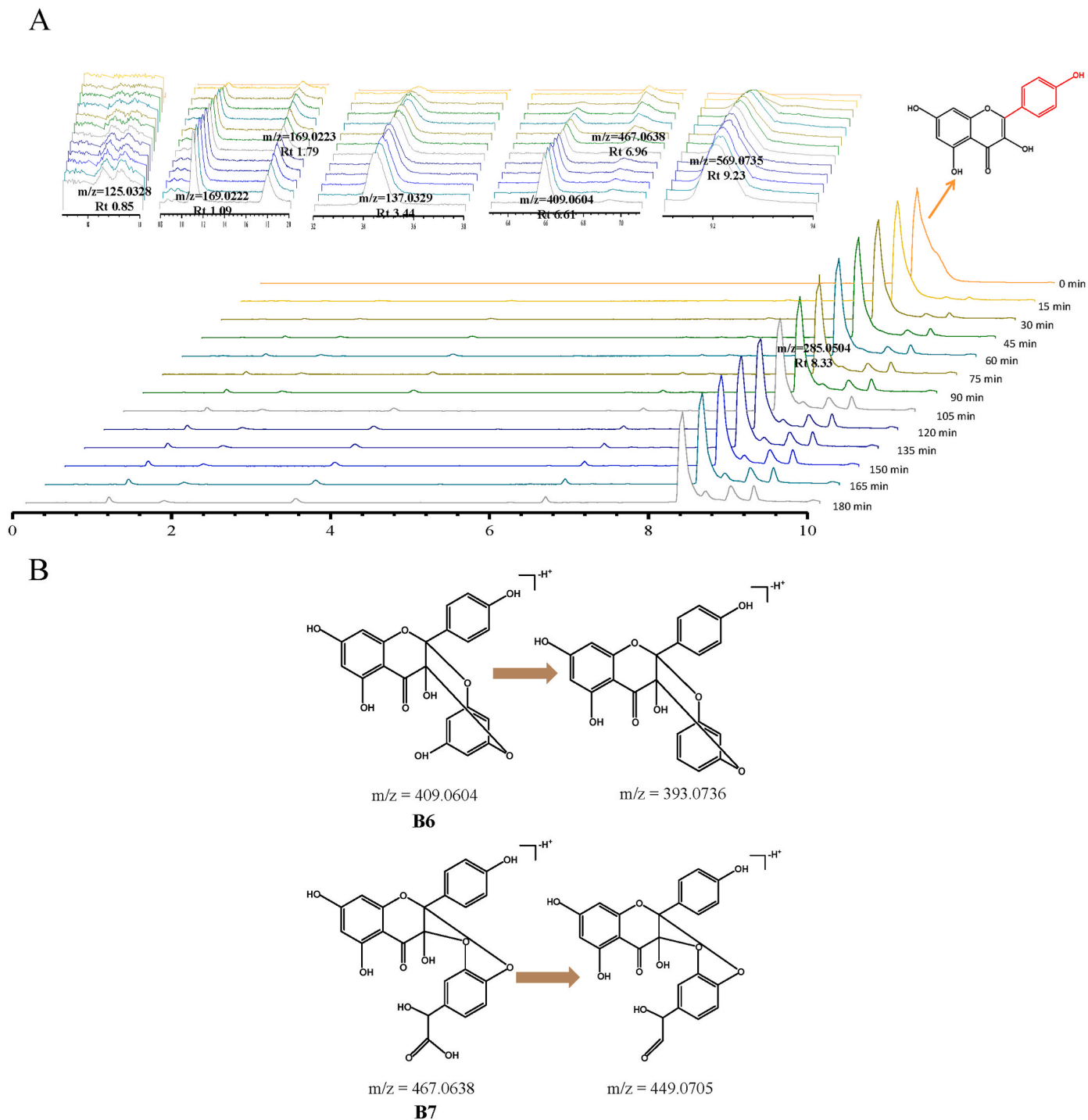
Fig. 5. (A) TIC chromatograms of kaempferol in boiling water. (B) Fragmentation scheme of kaempferol degradation products.
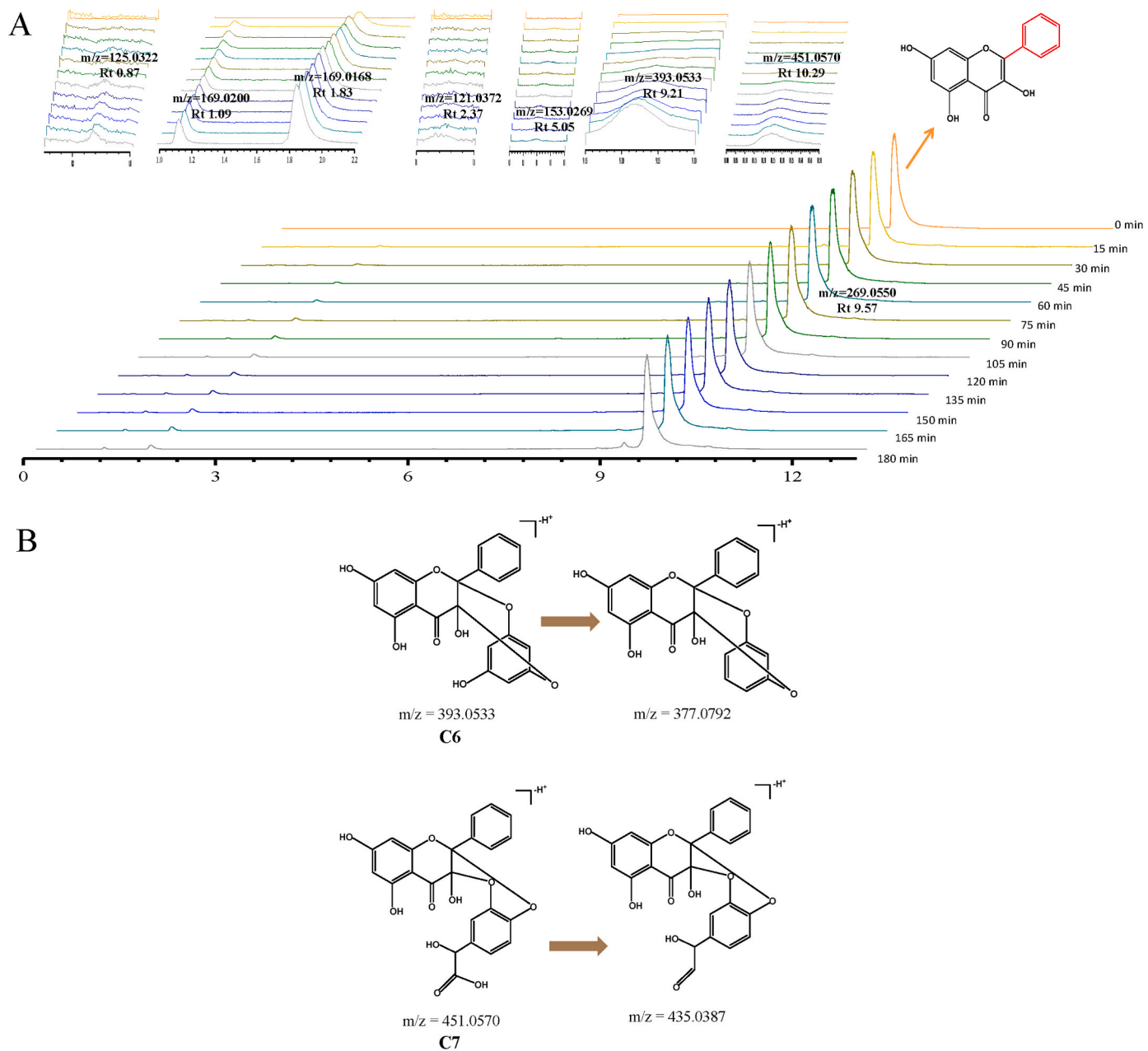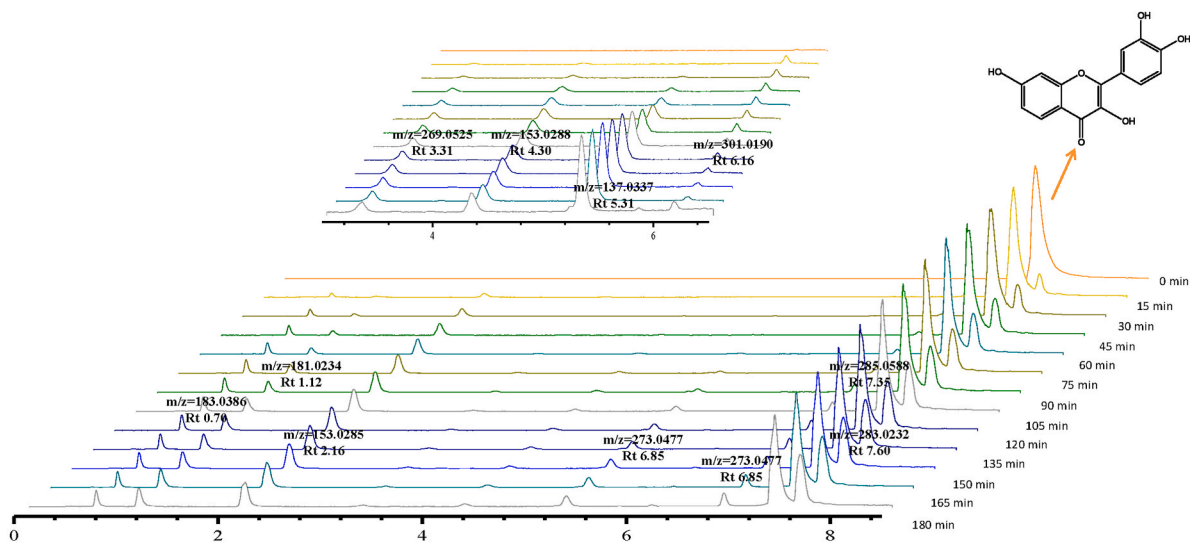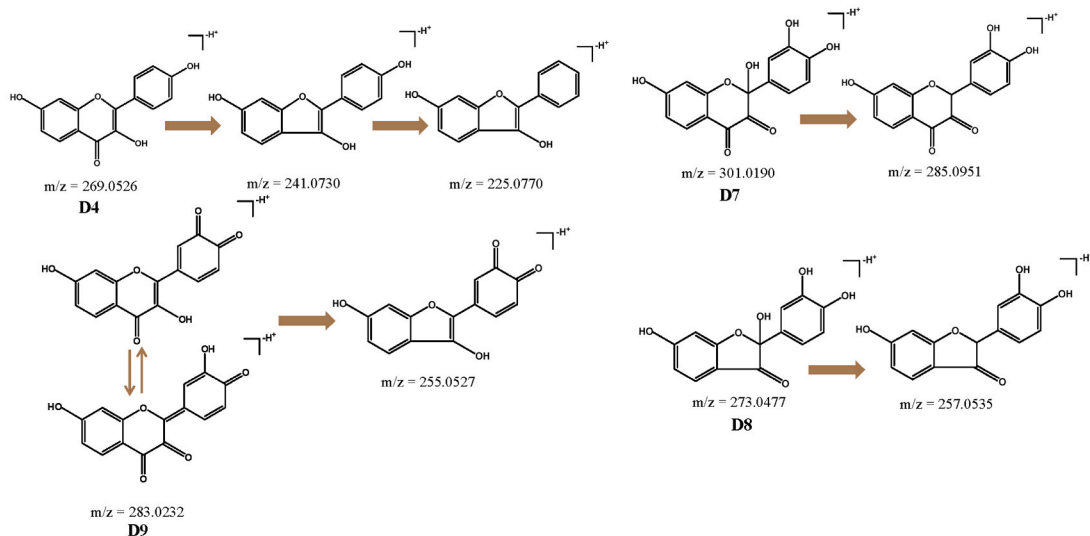
Fig. 6. (A) TIC chromatograms of galangin in boiling water. (B) Fragmentation scheme of galangin degradation products.
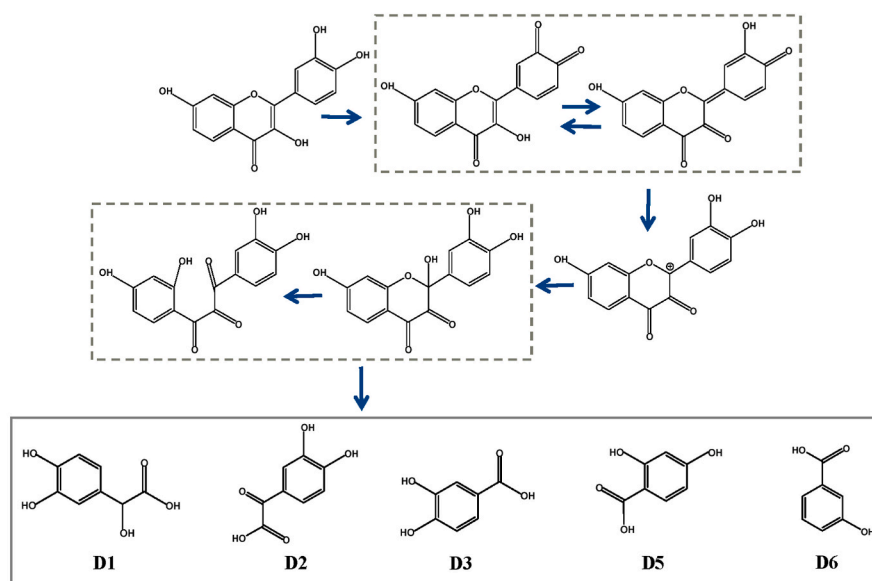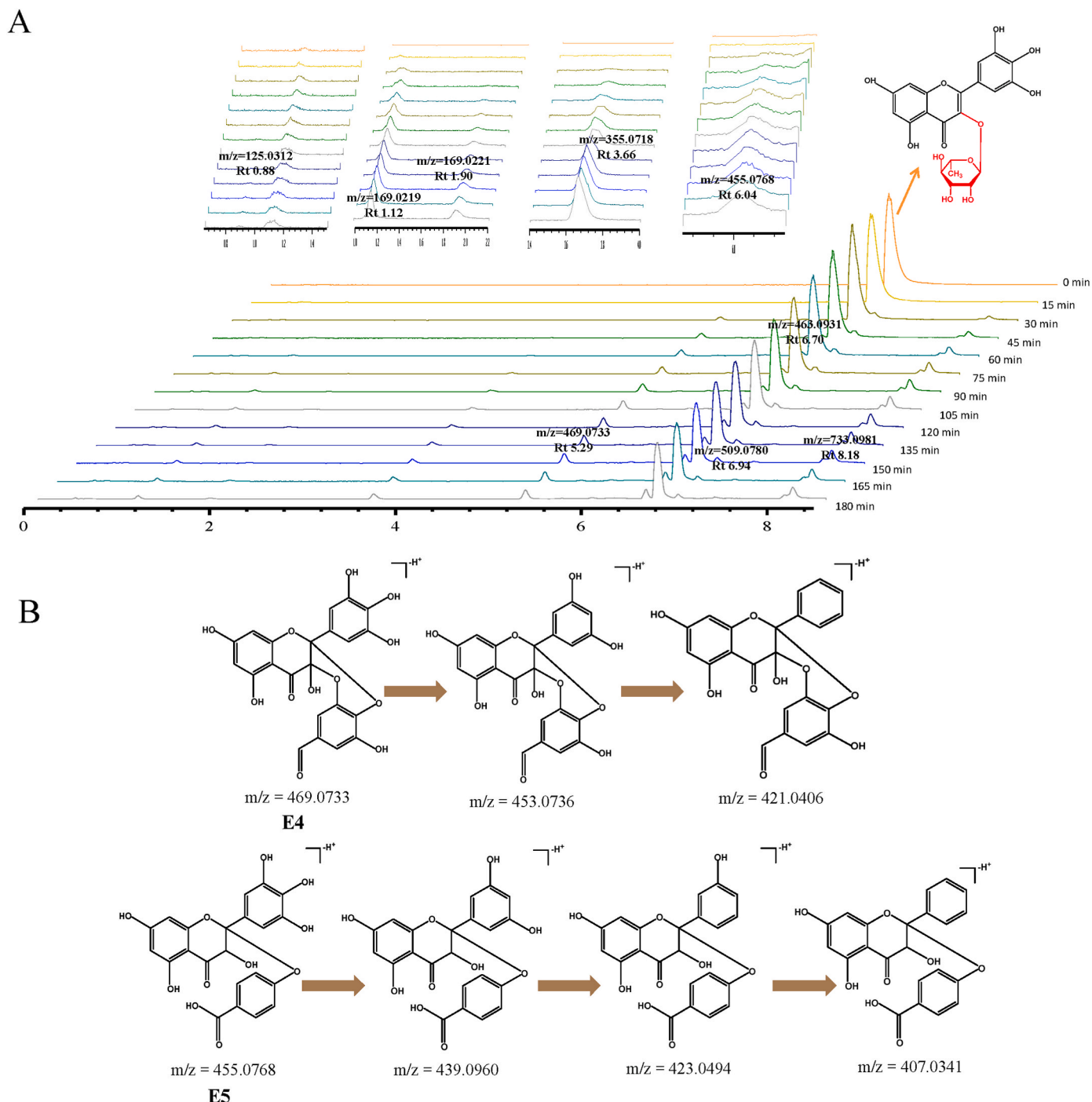
Fig. 7. (A) TIC chromatograms of fisetin in boiling water. (B) Fragmentation scheme of fisetin products. (C) Oxidative reaction pathway for degradation of fisetin.

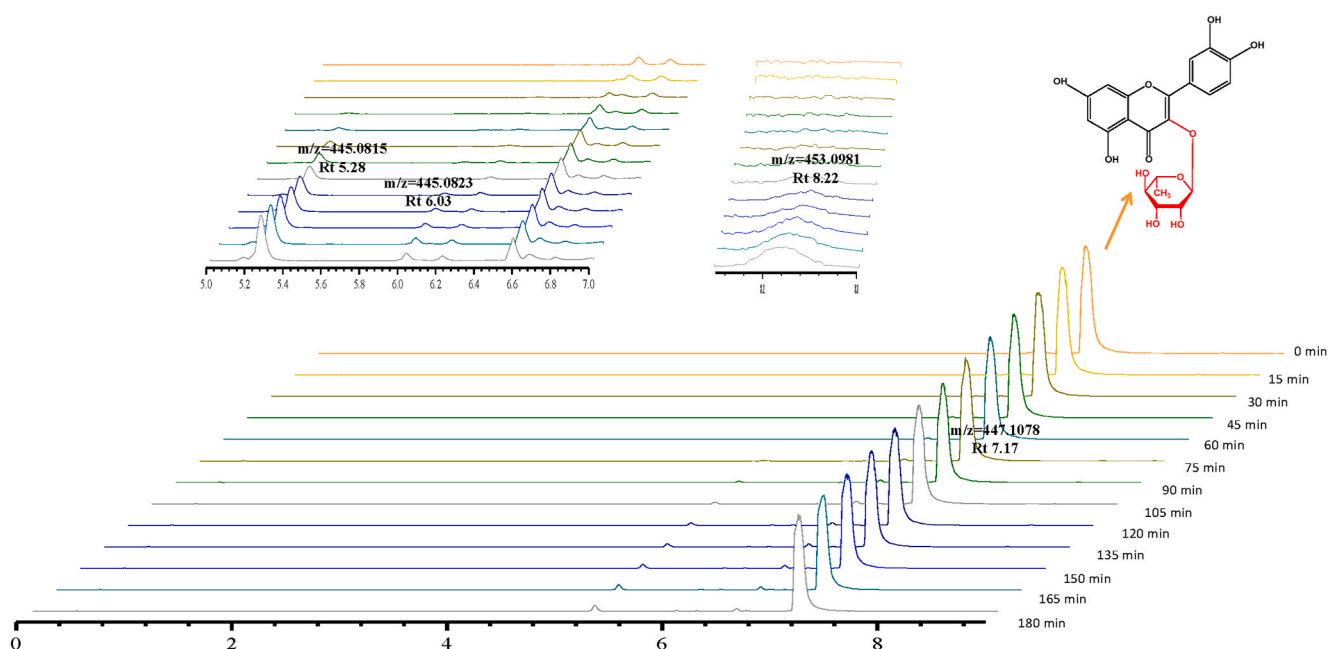Fig. 8. (A) TIC chromatograms of myricitrin in boiling water. (B) Fragmentation scheme of myricitrin products.

Compound B8 with m/z 569.0735 included m/z 551.0902, m/z 499.0782, m/z 311.0419, m/z 257.0656, m/z 239.0547 and m/z 151.0201, which indicated the existence of kaempferol core structure. Compound B8 maybe a kaempferol dimer formed by opening the carbon-carbon double bond of the ring C of kaempferol and oxidative polymerization with another kaempferol. Interestingly, kaempferol did not undergo hydroxylation on the ring C as for myricetin in water. The presence of a catechol unit on ring B and a free C-3 hydroxyl groups appear to be a prerequisite for the formation of ring C carbocation in the oxidative decomposition of flavonols (Krishnamachari et al., 2002). A poorly substituted flavonols on ring B skeleton are not able to form o-quinone (Krishnamachari et al., 2004). It may explain why no

hydroxylation products and quinones of kaempferol were observed in boiling water.

3.4. Identification of new products of galangin in boiling water

Galangin was the most stable one among the seven flavonols, and its degradation trend in boiling water was shown in Fig. 6A. The degradation products of galangin in boiling water were identified as 1,3,5-benzenetriol (C1, m/z 125.0322), 3,4,5-trihydroxybenzoic acid (C2, m/z 169.0222), 2,4,6-trihydroxybenzoic acid (C3, m/z 169.0168), benzoic acid (C4, m/z 121.0372) and 2,4,6-trihydroxybenzaldehyde (C5, m/z 153.0269). Galangin showed the similar oxidative
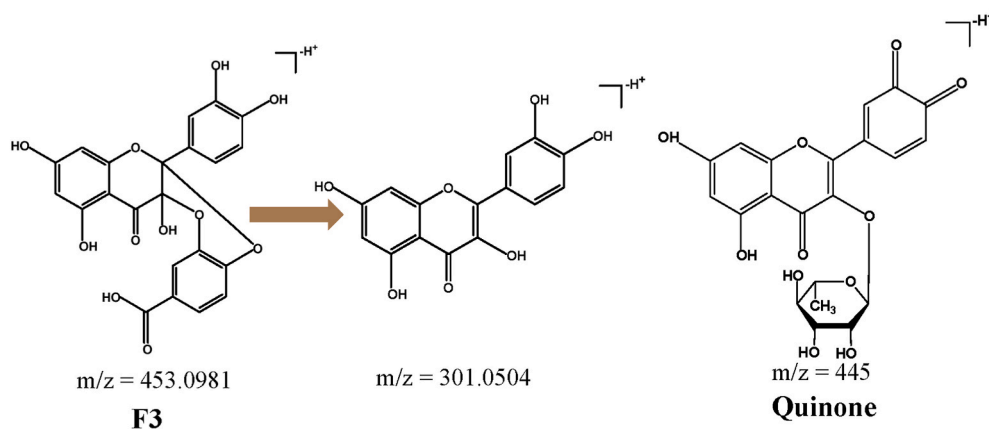
A

B

Fig. 9. (A) TIC chromatograms of quercitrin in boiling water. (B) Fragmentation scheme of quercitrin products.

degradation with kaempferol to form the compound C6 (m/z 393.0533) and compound C7 (m/z 451.0570), which were 124 and 181 Da more than the original substance, respectively. Compound C6 may contain an phloroglacinol molecule, and compound C7 may be that galangin bound the 3,4-dihydroxymandelic acid at the C2, C3 positions of the ring C.

3.5. Identification of new products of fisetin in boiling water

When fisetin was heated in boiling water, the new degradation products were observed as 3,4-dihydroxymandelic acid (D1, m/z 183.0386), 3,4 -dihydroxyphenylglyoxylate (D2, m/z 181.0232), protocatechuic acid (D3, m/z 153.0288), 2,4-dihydroxybenzoic acid (D5, m/z 153.0288) and 3-hydroxybenzoic acid (D6, m/z 137.0336) (Fig. 7A). 3,4-dihydroxymandelic acid and protocatechuic acid were also found in case of quercetin in boiling water (Lin et al., 2022). Comparing the chemical structures of fisetin and quercetin, the number of hydroxyl groups in ring A of fisetin and quercetin were different, but the structure of ring B was the same. In addition, were also observed. For compound D4 (m/z 269.0526), which was 16 Da less than fisetin, suggesting that it might undergone a dehydroxylation. The mass spectra of

compound D7 (301.0190 m/z) was 16 Da more than that of fisetin, it may be the product of the hydroxylation of fisetin. But it was worth noting that the water adducts with the introduction of a hydroxyl group was not stable and continues to undergo intramolecular rearrangements or tautomerization (Zhou et al., 2007). Compound D8 (m/z 273.0477) had 28 Da less than D7, which may be a product of decarbonylation of the unstable intermediate D7. As for compound D9 (m/z 283.0232), based on the main oxidation pathway of flavonols, it was fisetin deprotonated to form quinones. According to the above new product characterization (Cao et al., 2020), the possible degradation mechanism of fisetin in boiling water was shown in (Fig. 7C).

3.6. Identification of new products of myricitrin, quercitrin and rutin in boiling water

The degradation process of myricitrin, quercitrin and rutin in boiling water were shown in Figs. 8A, 9A and 10A. Firstly, 1,3,5-benzenetriol (E1, m/z 125.0288), 3,4,5-trihydroxybenzoic acid (E2, m/z 169.0218) and 2,4,6-trihydroxybenzoic acid (E3, m/z 169.0214) were observed in myricitrin, which were also found in myricetin. In addition, E4 (m/z
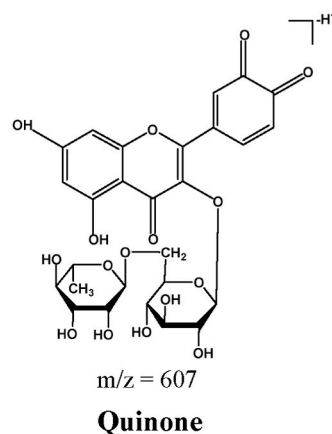
A
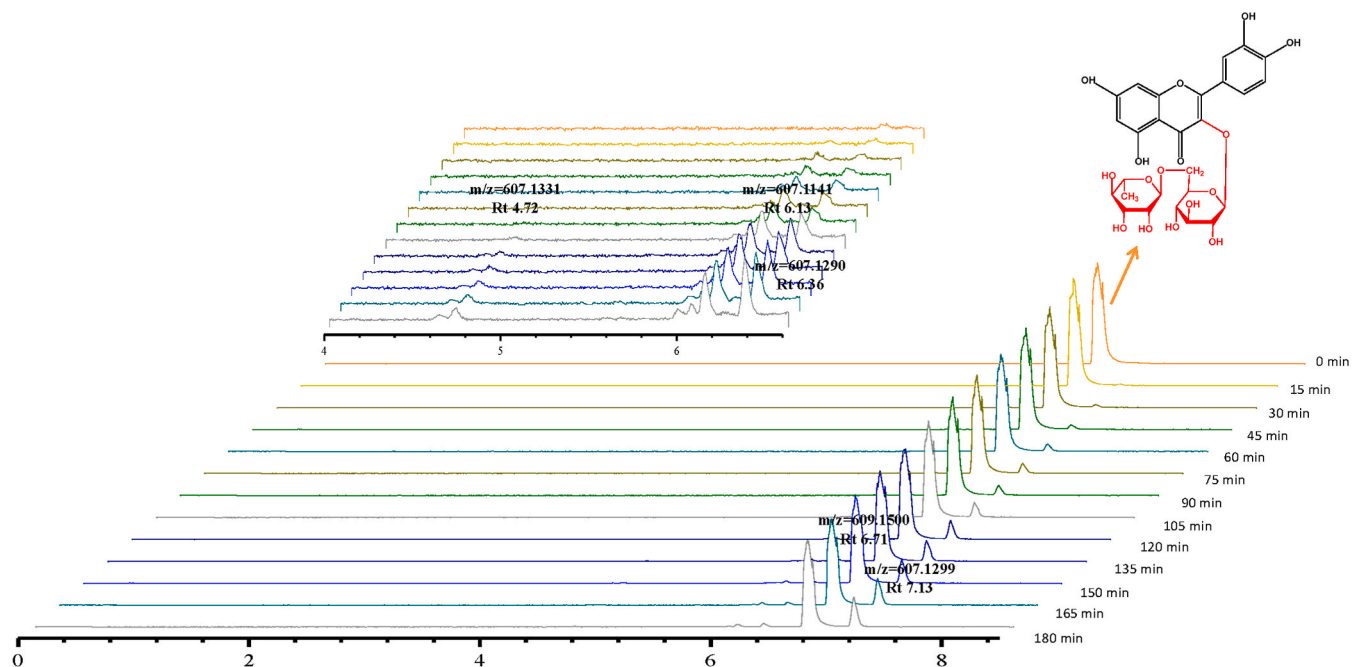
B

Fig. 10. (A) TIC chromatograms of rutin in boiling water. (B) Degradation product of rutin.

469.0733) and E5 (m/z 455.0768) were observed, their m/z values were 152 Da and 138 Da more than myricetin, which may be myricitrin lost the rhamnose group, and then linked with 3,4,5-trihydroxybenzalde-hyde and 4-hydroxybenzoic acid (Fig. 8B). Quercitrin and rutin were much more stable in boiling water than that of quercetin, and the glycosylation of 3-OH significantly improved the oxidability of flavonols in boiling water. Therefore, in boiling water, the deprotonation process of quercitrin and rutin was mainly observed, and the corresponding quinones were generated. Due to its more complex structure, rutin with a two-part glycoside on the C-3 position has more isomers. During the heating process, rutin was oxidized to form four quinones, compound G1 (m/z 607.1331), G2 (m/z 607.1141), G3 (m/z 607.1290) and G4 (m/z 607.1299), which were similar to that observed by Olivier Dangles et al. (Dangles et al., 1999). However, because these compounds have many possible deprotonation sites to form various isomers.

4. Conclusion

In this study, the stability of seven polyhydroxy flavonols in boiling water was analyzed by UPLC-MS/MS. According to their structure, flavonols were more or less sensitive to heat treatment. Hydroxylation of flavonols at the ring B usually weakened their stability, but hydroxyl-ation at the ring A will increase its stability. Glycosylated flavonols were more resistant to heat treatment than their aglycon form. During the boiling process, flavonols underwent a series of chemical reactions, such as hydroxylation, dehydroxylation, deglycosidation, deprotonation, and C-ring cleavage. The major products were found to be 1,3,5-benzene-triol, 2,4,6-trihydroxybenzoic acid and 2,4,6-trihydroxybenzaldehyde, dimers and quinones, etc. It was worth noting that most of these degradation products were active substances with excellent antioxidant properties. Our results may provide deeper insights into their subse-quent complex biological activities.

CRediT authorship contribution statement

Shiye Lin: Investigation, Data curation, Writing – original draft. **Jesus Simal-Gandara:** Formal analysis, Data curation. **Hui Cao:** Writing – review & editing, Supervision. **Jianbo Xiao:** Funding acqui-sition, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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