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Application of Direct Infusion Electrospray Ionization Quadrupole Time-of-Flight Mass Spectrometry in Qualitative Analysis of Sixteen Compounds From Traditional Chinese Medicine

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Abstract: Direct infusion (DI) electrospray ionization quadrupole time-of-flight (Q-TOF) mass spectrometry was applied to analysis sixteen compounds from traditional Chinese medicines (TCMs). Characteristics of these compounds in electrospray ionization mass spectrometry (ESI-MS) and in MS/MS were observed to know the differences of ionization capacity and dissociation characteristics of structurally different compounds. The observation indicated that in order to maximize numbers of constituents detected, it is necessary to analyze sample in both positive and negative mode. The existence of carbonyl group in structure seems to be a factor that favors the formation of quasi-molecular ion (QMI) or other adduct molecular ion (OAMI) in positive mode. When cone voltage was 30V, most compounds could form mass spectral peaks of QMIs or OAMIs. However, in-source collision-induced dissociation (CID) seemed unable to be completely avoided by altering cone voltage. Analysis was recommended at three different cone voltages of 10V, 30V and 50V. MS/MS was proved to be an effective way to obtain additional structural information because fragment ions were observed for all QMIs and OAMIs in MS/MS. The developed method has been successfully applied in our study on Si-Wu-Tang. The method is useful for quick qualitative analysis of constituents in mixture samples of TCM.

Key words: traditional Chinese medicine; electrospray ionization; direct infusion; time-of-flight; qualitative analysis
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直接输注电喷雾电离四极杆飞行时间质谱在十六种中药来源化合物定性分析中的应用

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摘要: 采用直接输注电喷雾电离质谱对十六种中药来源的化合物进行了分析。观察了它们的电喷雾电离质谱和串联质谱特征, 以了解不同结构化合物的电离能力和裂解特点。观察表明: 为使样品成分尽可能多地被

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检测，必须同时进行正负两种模式的分析。化合物结构中羰基的存在似有利于化合物在正离子模式下形成准分子离子或其它分子加和离子。当采样锥电压为30 V时，大多数化合物能形成准分子离子或其它分子加和离子。但改变采样锥电压似不能完全避免源内裂解。建议分析时同时考察不同采样锥电压(如10 V、30 V和50 V)。串联质谱分析被证明是获得进一步结构信息的有效手段，因为对于所有被观察的准分子离子和其它分子加和离子，均能在串联质谱分析中检测到碎片离子。本研究在四物汤的研究中已经成功地运用了该方法。此方法有助于中药混合物中样品成分的快速定性分析。

关键词：中药；电喷雾电离；直接输注；飞行时间；定性分析

The efficacy of traditional Chinese medicine (TCM) has led to research efforts both inside and outside China[1~10]. The chemical nature of TCM is a kind of basically complex mixture of natural products, the majority of which are plant metabolites. A crux of researching TCM is to find out the compound or group of compounds that is responsible for the drug's efficacy. If this goal was achieved, the quality control of drug could be more efficiently performed and new drugs with enhanced therapeutic effects could be expected. However, searching effective constituents from complex mixture means large amount of work of chemical separation and pharmacological screening. For such a complicated, laborious and time-consuming process, early and promptly acquisition of qualitative information about the composition of extracts or fractions from TCMs may help the researchers to design the best research procedure, and therefore to simplify and accelerate the research process.

Mass spectrometry (MS), with its high sensitivity and capability of providing M_r and additional structural information[11], is a very important technique for qualitative analysis. Currently, the chromatographic techniques coupled with MS, such as GC/MS and LC/MS, have frequently been employed to study the composition of complex mixtures. The application of GC/MS is relatively limited due to its critical requirement of sample's volatility and thermal stability[12]. Contrarily, LC/MS has no such limitation and has been successfully used to analyze many types of mixtures such as combinatorial libraries[13, 14] and botanical extracts[15]. However, for TCM research, the application of LC/MS is still little, while GC/MS is frequently employed to analyze the composition of essential oils.

Electrospray ionization (ESI) is one of the most important interfaces employed in LC/MS. An outstanding characteristic of ESI is that the amount of internal energy imparted to generated ions is the lowest in all mass spectrometric ionization techniques and an extremely low degree of fragmentation is inherent to the ESI process[16]. An interesting result of this "soft" characteristic of ESI is that useful information on composition of mixture sample can be obtained using direct infusion (DI) or flow injection (FI) method without chromatographic separation. Theoretically, in such ESI mass spectra of mixtures, many of the major mass spectral peaks should be quasi-molecular ions (protonated or deprotonated molecules) or other adduct molecular ions (sodium, potassium, ammonium adduct, etc.) of the mixture's constituents. Thus, molecular mass information of the constituents can be obtained. Using mass spectrometers with high resolution, elemental compositions of compounds can be determined. Furthermore, tandem mass spectrometry (MS/MS) can be used as an additional aide to elucidate the structure of compounds, through it has the tendency to form structurally significant fragment ions[14]. DI ESI-MS method has been applied to analyze medicinal plant extracts and wines[17~19].

However, in comparison with LC/MS, DI and FI ESI-MS methods have two major disadvantages due to the complete co-elution of all sample components. Firstly, it cannot differentiate isomeric ions. Secondly, ion suppression effect may cause some constituents undetectable[19]. Nevertheless, a significant advantage possessed by DI and FI methods is simplicity and speed of operation. In LC/MS, effort has to be made to choose a suitable mobile phase, which satisfies requirements of both separation and ionization. Good condition for ionization is not always good for separation. In contrast, no such effort is necessary for DI or FI. Acid, alkali and other agents can be added to help ionization as needed. Furthermore, another advantage of DI and FI is that observation of an ion by MS can be performed as long as desired[20], provided the sample is of enough amounts. This is especially favoring when performing tandem mass spectrometry for additional information.

In this paper, the application of DI ESI-MS method in sixteen compounds from TCMs using Quadrupole time-of-flight (Q-TOF) mass spectrometer is reported, which has the potential of accurate mass measurements. The compounds will be analyzed in different detection mode and at different cone voltages. MS/MS were performed for major quasi-molecular ions or other adduct molecular ions detected. The finally developed method has been applied to our study on Si-Wu-Tang and provided useful information.

1 MATERIALS AND METHODS

1.1 Chemicals and Drugs

1, 4-linked pentaglucoside and timosaponin A-Ⅲ were obtained from Professor Baiping Ma, and puerarin from Professor Lin Wang. Sucrose was of analytical grade. Magnolol, ferulic acid, astragaloside Ⅳ, oxymatrine, catalpol, tetramethyl pyrazine hydrochloride, 1, 8-dihydroxy anthraquinone, scoparone, kaempferol, ginkgolide A, (+)-catechin, and paeoniflorin were purchased from China National Institute for the Control of Pharmaceutical and Biological Product. Water treated with Millipore water purification system and HPLC grade acetonitrile were used as sample solvents for mass spectrometry. All other agents were of analytical grade.

1.2 DI ESI-MS and MS/MS Observation of 16 Plant Metabolites

Mass spectrometric measurements were performed on a Q-TOF2 nanospray electrospray ionization tandem mass spectrometry system (Micromass UK Limited) with direct infusion in both positive and negative mode. Capillary voltage was 3 000V. MCP detector voltage was 2 200V. Source tempreture was 80℃. For positive mode analysis, compounds were dissolved in 50% acetonitrile solution containing 0.1% of formic acid. For negative mode analysis, compounds were dissolved in 50% acetonitrile solution containing 1% of ammonia. All sample concentrations were in the rang from 5 to 10mg/L with the exception of 1, 4-linked pentaglucoside, the concentration of which was increased to 40mg/L in order to obtain sufficient signal intensity. The final mass spectra were obtained by combining single-scan ion chromatogram until the intensity of base peak reached 10^3 or 10^4 counts. ESI-MS observations were performed under a series of cone voltages (10V, 30V, 50V and 70V) and collision energy of 10eV. MS/MS of quasi-molecular ions or other adduct molecular ions were performed under different collision energy (not exceeding 70eV), and MS/MS spectra with maximized fragment information were recorded.

2 RESULT AND DISCUSSION

2.1 Detection Mode

For DI ESI-MS analysis of mixtures, our primary goal for method development is to maximize the numbers of constituents detected as quasi-molecular ions or other adduct molecular ions, at the same time, minimize in-source collision-induced dissociation (CID). From this point, "quasi-molecular ion" and "other adduct molecular ion" were abbreviated as "QMI" and "OAMI", respectively. The selected 16 compounds cover most frequently seen structural types of plant metabolites (see Table 1). In our observation formation of QMI or OAMI species of all 16 compounds were detected (see Table 1). But oxymatrine, tetramethyl pyrazine hydrochloride and scoparone formed QMIs or OAMIs only in positive mode, while in negative mode only weak and noisy peaks could be observed. Conversely, ferulic acid formed QMI only in negative mode (see Table 1), and no QMI or OAMI observed in positive mode. For (+)-catechin, magnolol, paeoniflorin, catalpol, astragaloside Ⅳ, 1, 4-linked pentaglucoside, sucrose, 1, 8-dihydroxy anthraquinone and timosaponin A-Ⅲ, the relative abundance of QM I or OAM I peaks in negative-ion mass spectra was much more than that founded in positive-ion mass spectra. For kaempferol, characteristic was the opposite. These demonstrate that the capacities of forming QM Is or OAM Is in two detection modes of structurally different plant metabolites are quite different. Therefore, in order to maximize numbers of constituents detected, it is necessary to analyze sample in both positive and negative mode.

Table 1 Structural types and QM I or OAM I species observed of 16 compounds

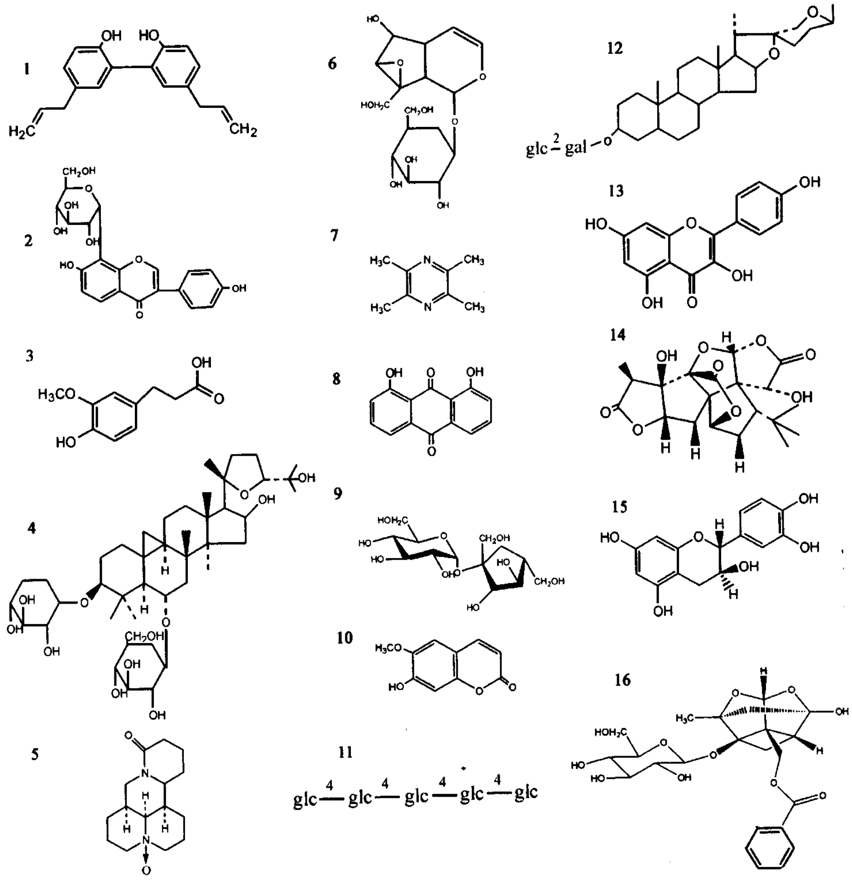
No.	Compound	Structural type	QM I or OAM I species observed: Positive mode (m/z)	QM I or OAM I species observed: Negative mode (m/z)
1	magnolol (M_n= 266)	lignan	267 $[M+H]^+$, 284 $[M+NH_4]^+$	265 $[M-H]^-$
2	puerarin (M_n= 416)	isoflavone	417 $[M+H]^+$	415 $[M-H]^-$
3	ferulic acid (M_n= 194)	acid	-	193 $[M-H]^-$
4	astragaloside Ⅳ (M_n= 784)	triterpenoid saponin	785 $[M+H]^+$	783 $[M-H]^-$
5	oxymatrine (M_n= 264)	alkaloid	265 $[M+H]^+$, 529 $[2M+H]^+$	-
6	catalpol (M_n= 362)	glycoside (iridoid glycoside)	385 $[M+Na]^+$, 380 $[M+NH_4]^+$, 401 $[M+K]^+$	361 $[M-H]^-$, 723 $[2M-H]^-$
7	tetramethyl pyrazine hydrochloride (M_n= 136)	alkaloid	137 $[M+H]^-$	-
8	1, 8-dihydroxy anthraquinone (M_n= 240)	anthraquinone	241 $[M+H]^+$	239 $[M-H]^-$
9	sucrose (M_n= 342)	disaccharide	365 $[M+Na]^+$, 381 $[M+K]^+$	341 $[M-H]^-$
10	scoparone (M_n= 206)	coumarin	207 $[M+H]^+$	-
11	1, 4-linked-pentaglucoside (M_n= 828)	oligosaccharide	829 $[M+H]^+$, 434 $[M+K+H]^{2+}$	827 $[M-H]^-$
12	timosaponin A-Ⅲ (M_n= 740)	steroidal saponin	741 $[M+H]^+$, 758 $[M+NH_4]^+$	739 $[M-H]^-$
13	kaempferol (M_n= 286)	flavonoid (flavonol)	287 $[M+H]^+$	285 $[M-H]^-$
14	ginkgolide A (M_n= 408)	terpinoid (bicyclic diterpenoid)	409 $[M+H]^+$, 426 $[M+NH_4]^+$	425 $[M+H_2O-H]$ 407 $[M-H]^-$
15	(+)-catechin (M_n= 290)	flavonoid (flavan-3-ol)	291 $[M+H]^+$	289 $[M-H]^-$
16	paeoniflorin (M_n= 480)	glycoside (bicyclic terpenoid glycoside)	498 $[M+NH_4]^+$, 503 $[M+Na]^+$	479 $[M-H]^-$

As generally recognized, alkaloids and other compounds containing nitrogen atom have tendency to form positive QM I ($[M+H]^+$) due to the high proton affinity of nitrogen atom. In accordance with this in our study, two nitrogen containing compounds, oxymatrine and tetramethyl pyrazine hydrochloride, gave base peak QM I in positive-ion spectra and very little other peaks, while no QM I or OAM I was observed in negative mode. Interestingly scoparone, a compound does not contain any nitrogen atom, showed the same characteristic. It is much more interesting to compare the characteristics between (+)-catechin and kaempferol. Their structures are very similar with the major difference in that kaempferol contains carbonyl group while (+)-catechin does not (see Scheme 1 compound 13 and 15). In our observation, QM I peak of (+)-catechin in negative-ion spectrum (m/z 289, $[M-H]^-$) was base peak while in positive-ion spectrum only a very weak m/z 291 was detected, which might be QM I ($[M+H]^+$) of it (see Figure 1a and 1b). Conversely kaempferol formed base peak QM I ($[M+H]^+$, m/z 287) in positive-ion spectrum while in negative-ion spectrum QM I ($[M-H]^-$,

m/z 285) was not base peak (see Figure 1c and 1d). It seems that the existence of carbonyl group in structure helps QM I or OAM I formation in positive mode. An additional proof is that among the 16 plant metabolites all compounds possessing carbonyl group, including scoparone, kaempferol, ginkgolide A, puerarin, paeoniflorin and 1, 8-dihydroxy anthraquinone, formed QM Is or OAM Is in positive mode (see Table 1).

2.2 Cone Voltage

When cone voltage was increased to 70V, the spectra of most compounds, in positive or negative mode, showed increased relative abundance of in-source CID fragment ion peaks and decreased relative abundance of QM I or OAM I peaks. A few compounds such as kaempferol, 1, 8-dihydroxy anthraquinone and tetramethyl pyrazine hydrochloride in positive mode, timosaponin A-III in negative mode, and sucrose in both positive and negative mode formed more stable QM Is or OAM Is, and little fragment ion peak was found at 70V cone voltage. These show that 70V cone voltage cause significant in-source CID for many plant metabolites.



Scheme 1　Structures of sixteen compounds

1—magnolol; 2—puerarin; 3— ferulic acid; 4—astragaloside Ⅳ; 5—oxymatrine; 6—catalpol; 7—tetramethyl pyrazine hydrochloride; 8—1, 8-dihydroxy anthraquinone; 9—sucrose; 10—scoparone; 11—1, 4-linked-pentaglucoside; 12—timosaponin a-III; 13—kaempferol; 14—ginkgolide A; 15— (+)-catechin; 16—paeoniflorin

Generally as observed, decreased cone voltage caused decreased in-source CID. For catalpol in negative-ion spectra, the abundance ratio between fragment ion peak (m/z 199) and QM I ($[M-H]^-$, m/z 361) peak was significantly decreased when cone voltage was shifted from 30V to 10V (see Figure 2). However, for most compounds, when cone voltage was decreased to 10V, the relative abundance of QM I or OAM I peaks also decreased and more background ion peaks could be seen, which indicates the lost of sensitivity. More unfortunately, for astragaloside IV, timosaponin A-III, and paeoniflorin in positive mode, catalpol and kaempferol in negative mode, significant fragment ion peaks were observed even at 10V cone voltage. This demonstrates that many plant metabolites form extremely unstable QMIs or OAMIs in ESI, and in-source CID are unable to be completely avoided by decreasing cone voltage.

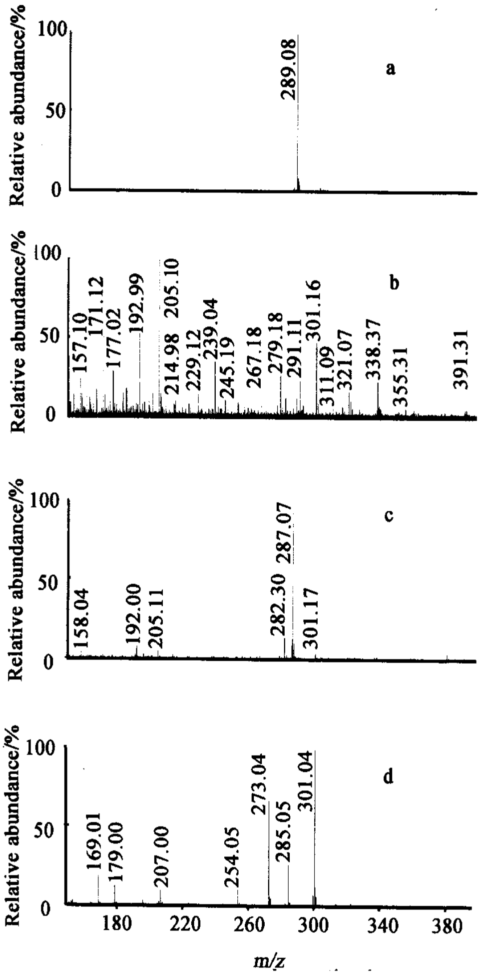


Fig 1 Positive-ion and negative-ion mass spectra of (+)-catechin and kaempferol (cone voltage= 30V)

a—Negative-ion mass spectrum of (+)-catechin;
b—Positive-ion mass spectrum of (+)-catechin;
c—Positive-ion mass spectrum of kaempferol;
d—Negative-ion mass spectrum of kaempferol

2.3 In-source CID at 30V Cone Voltage

When cone voltage was 30V, significant in-source CID fragment ions were observed only with magnolol, astragaloside IV and timosaponin A-III in positive mode, ferulic acid and catalpol in negative mode and paeoniflorin in both modes. The relative abundance of these in-source CID fragment ion peaks was lower than that of QMI or OAMI peaks except for catalpol in negative mode and paeoniflorin in positive mode, while the relative abundance of fragment ion peaks (m/z 199 in catalpol and m/z 179 in paeoniflorin) was higher than that of QMI or OAMI peaks. These indicate that although in-source CID was unable to avoid, it does not impede that most plant metabolites form QMIs or OAMIs as base peak when cone voltage was 30V. Even if QMIs or OAMIs were not base peaks for a minority of compounds, their QMIs or OAMIs signals should not be very difficult to be detected.

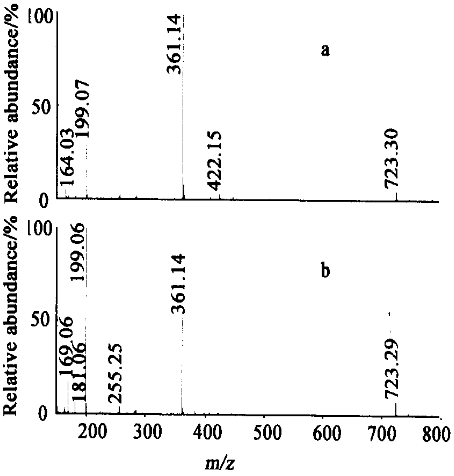


Fig 2 Negative-ion mass spectra of catalpol

a—Cone voltage= 10V; b—Cone voltage= 30V

2.4 MS/MS

For each QMI or OAMI, MS/MS was performed to see whether additional structural information could be obtained. As expected, all QMIs or OAMIs formed fragment ions in MS/MS, with collision energies used not exceeding 70eV. The major fragment ions observed were listed in Table 2. Therefore, MS/MS is an effective way to obtain further structural information of QMIs or OAMIs. For most compounds, fragmentation pattern of in-source CID and MS/MS were similar. But for 1, 4-linked pentaglucoside in negative mode, the fragment ions in MS/MS were m/z 708, 666, 504 and 341, while in-source CID fragment ions were

m/z 707, 665, 545, 503 and 341. The reason for the difference is not clear.

Table 2 Major fragment ions in MS/MS of sixteen compounds

No.	Compounds	Positive mode (m/z)		Negative mode (m/z)	
		Precursor ions	Major fragments in MS/MS	Precursor ions	Major fragments in MS/MS
1	magnolol (M_n = 266)	267 $[M+H]^+$	239, 226, 211, 197	265 $[M-H]^-$	247, 245
2	puerarin (M_n = 416)	417 $[M+H]^+$	399, 381, 363, 351, 335, 327, 321, 307, 297, 267, 255	415 $[M-H]^-$	295, 267
3	ferulic acid (M_n = 194)	-	-	193 $[M-H]^-$	149, 134
4	astragaloside IV (M_n = 784)	785 $[M+H]^+$	749, 767, 635, 605, 587, 569, 473, 455, 437, 419, 401	783 $[M-H]^-$	652, 622, 489, 179, 161, 149, 143, 131, 119, 113, 107, 101, 89, 71
5	oxymatrine (M_n = 264)	265 $[M+H]^+$	247, 205, 148, 136	-	-
6	catalpol (M_n = 362)	385 $[M+Na]^+$	323, 203, 185, 155, 143	361 $[M-H]^-$	199, 181, 169, 137, 127, 97
7	tetramethyl pyrazine hydrochloride (M_n = 136)	137 $[M+H]^+$	122, 96, 80, 69, 55	-	-
8	1,8-dihydroxy anthraquinone (M_n = 240)	241 $[M+H]^+$	223, 213, 195, 185, 167, 157, 139, 128, 121, 115	239 $[M-H]^-$	211, 183, 167, 139
9	sucrose (M_n = 342)	365 $[M+Na]^+$	203, 185	341 $[M-H]^-$	179, 161, 149, 143, 131, 119, 113, 107, 101, 89, 71
10	scoparone (M_n = 206)	207 $[M+H]^+$	191, 179, 163, 151	-	-
11	1, 4-linked-pentaglucoside (M_n = 828)	829 $[M+H]^+$	811, 667, 649, 505, 487, 343, 325, 163	827 $[M-H]^-$	708, 666, 588, 504, 444, 341, 281
		434 $[M+K+H]^{2+}$	353, 344, 272, 263, 254, 242, 191, 182		
12	timosaponin A-III (M_n = 740)	741 $[M+H]^+$	579, 417, 399, 325, 273, 163	739 $[M-H]^-$	577, 511, 457, 179, 161
		758 $[M+NH_4]^+$	741, 579, 417, 399, 325, 163		
13	kaempferol (M_n = 286)	287 $[M+H]^+$	258, 229, 213, 185, 171, 165, 157, 153, 147, 137, 121, 107, 93, 69	285 $[M-H]^-$	268, 255, 239, 227, 211, 187, 171, 159, 143, 131, 117, 108, 93, 83, 63
14	ginkgolide A (M_n = 408)	409 $[M+H]^+$	391, 373, 363, 355, 345, 327, 317, 309, 299, 281, 249, 113,	425 $[M+H_2O-H]^-$	407, 397, 381, 369, 363, 351, 335, 325, 307, 291, 101, 73
		426 $[M+NH_4]^+$	409, 391, 373, 363, 345, 327		
15	(+)-catechin (M_n = 290)	291 $[M+H]^+$	-	289 $[M-H]^-$	245, 271, 221, 203, 187, 179, 175, 165, 161, 151, 137, 125, 109, 97, 83
16	paeoniflorin (M_n = 480)	498 $[M+NH_4]$+	480, 463, 341, 319, 301, 285, 197, 179	479 $[M-H]^-$	449, 327, 121
		503 $[M+Na]^+$	381, 341, 217, 219, 205, 185, 179, 161, 151, 133, 105, 85		

2.5 The Developed Method

Based on our findings, the finally developed DIESI-MS method is to analyze sample in both positive and negative mode at three cone voltages (10V, 30V and 50V). 10V and 50V cone voltages are recommended because 10V cone voltage may help to minimize in-source CID for some unstable compounds and 50V cone voltage may increase sensitivity for some compounds. Then MS/MS should be performed for further structural information with the ions of interest and sufficient signal intensity at different collision energies, and spectra with maximized fragment information should be recorded. This method has been applied in our research of SI-WU-TANG, a traditional Chinese hematopoitics, and provided us important information on composition of its extracts or fractions[21, 22].

3 CONCLUSIONS

Our study suggested that ESI was an efficient ionization method for most plant metabolites from TCMs. All the selected compounds could form QMIs or OAMIs under our experimental conditions. Some compounds ionized more efficiently in positive mode and some compounds ionized more efficiently in negative mode. The existence of nitrogen atom and carbonyl group in structure seemed to favor QMI or OAMI formation in positive mode. Cone voltage should neither be very high due to significant increase of in-source CID nor be very low due to decrease of sensitivity. Analysis at a series of cone voltages (10V, 30V, 50V) was recommended. Despite the "soft" characteristic of ESI, in-source CID seemed unable to be completely avoided for some plant metabolites. Nevertheless for all compounds observed, in-source CID did not impede detection of QMIs or OAMIs when cone voltage was 30V. Our method has been successfully applied to provide qualitative information for TCM samples.

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精密度水平可以满足地质样品的高分辨同位素示踪及同位素定年的需要。

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