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A comparison of the chemical composition in *Salvia miltiorrhiza* Bunge from 5 different regions in Shaanxi province by direct injection ESI-Q-TOF-MS

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Abstract: Due to the advantages of scanning speed and high sensitivity, ESI-Q-TOF-MS is widely applicated to identify the chemical composition of traditional Chinese medicine. In addition, ESI-Q-TOF-MS can provide the precise mass number and possible element composition of fragmentation ions. Therefore, it can accurately evaluate the quality of *salvia miltiorrhiza* (Danshen) in different areas of Shaanxi province and provide the basis for quality control of Danshen. An direct injection ESI-Q-TOF-MS analysis method was developed to value the chemical composition in Danshen coming from Shangzhou, Luonan, Dali, Danfeng and Tongchuan in Shaanxi province. Through analyzing the MS abundance of water soluble and lipid soluble extracts, there is a obvious variation in chemical composition. The comparison among different abundance is benefit to select the optimum planting area of Danshen. Results show that all Danshen samples from 5 different locations have 9 kinds of lipid soluble chemical composition (Tanshinone I, Tanshinone ⅡA, Tanshinone ⅡB, Cryptotanshinone, Dihydrotanshinone, Danshenxinkun A, Danshenxinkun D, 2-Isopropyl-8 -methylphenanthrene-3,4-dione and 7-beta-hydroxy-8-13- abietadiene-11,12-dione) and 9 kinds of water soluble chemical composition (Danshensu, Caffeic acid, Ferulic acid, Rosmarinic acid, Prolithospermic acid, Lithospermic acid, Protocatechuic acid, Salvianolic acid A and Salvianolic acid B). The content of Danshensu, Lithospermic acid, Salvianolic acid B and Cryptotanshinone is higher than other chemical composition with a MS abundance of 30% at least. However, with the change of planting environment, the content of the same chemical constituents in Danshen varies greatly in different regions. Tanshinones with important biological activity more exist in Danshen coming from Shangzhou, especially the MS abundance of Tanshinone I is as high as 72.6%, which is much higher than that in other 4 regions ranging from 1.8% to 11.3%. According to the comprehensive comparison, the quality of Danshen is ranged by Shangzhou > Tongchuan > Dali> Luonan> Danfeng. The direct injection ESI-Q-TOF-MS method is not easily affected by the growth environment and extraction conditions of the medicinal materials. It provides a scientific, reliable and convenient way to evaluate the medicine quality and a new way to formulate the specifications and grades of traditional Chinese medicine. The system is not only suitable for the chemical composition of Danshen in Shaanxi province, but also easily transplanted and popularized in other Danshen planting places.

Key words: Danshen, ESI-Q-TOF-MS, chemical composition, abundance, medicine quality

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ESI-Q-TOF-MS 直接进样法比较陕西 5 个不同地区丹参的化学成分差异

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摘要：ESI-Q-TOF-MS 因其扫描速度快、灵敏度高等优点，在中药化学成分的鉴定中应用广泛，且能提供碎片离子的精确质量数及可能的元素组成，不易受到药材的生长环境、提取条件等因素的影响，能够较为准确评价陕西不同地区的丹参药材质量。该文采用 ESI-Q-TOF-MS 直接进样分析方法对陕西商州、洛南、大荔、丹凤和铜川等五个地区丹参的化学成分进行比较分析，通过丹参水溶性和脂溶性成分的质谱丰度差异评价不同地区丹参化学成分含量的变化，对不同产地丹参的化学成分进行鉴定，综合分析选出最优丹参种植产地。结果表明：五地丹参均含有丹参酮ⅡA、隐丹参酮、丹参酮Ⅰ、二氢丹参酮、丹参酚酮、次丹参醌、丹参醌Ⅱ等 9 种脂溶性化学成分和丹参素、咖啡酸、阿魏酸、迷迭香酸、原紫草酸、紫草酸、原儿茶醛、丹酚酸 A、丹酚酸 B 等 9 种水溶性化学成分，其中丹参素钠、紫草酸、丹酚酸 B 和隐丹参酮的含量普遍较高，质谱丰度均大于 30%。但是随着种植环境不同，不同地区丹参的化学成分含量差异很大，如商州产丹参中含有较多具有生物活性的丹参酮类物质，其中丹参酮Ⅰ含量远远高于其他四个产地，质谱丰度达到 72.6 %，而其他地区丹参酮Ⅰ的质谱丰度仅为 1.8-11.3 %。研究表明，丹参质量按照地区排序为商州>铜川>大荔>洛南>丹凤。该方法为中药药材质量评价提供了科学、可靠、便捷的途径，为药材规格等级的制定提供了新的途径，为陕西丹参种植区域的选择提供重要信息。

关键词：丹参，ESI-Q-TOF-MS，化学成分，丰度，药材质量

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The dry root and rhizome of *Salvia miltiorrhiza* Bunge (red sage, family Labiatae) , known as “Danshen” in Chinese (Pharmacopoeia of the People’s Republic of China, 2015), is widely used as medicine in China and the neighboring countries for hundreds of years. The extracts are important in clinic medicine preparations, especially in the traeatment of cardiovascular diseases (Feng et al, 2017). Danshen also has a good therapeutic effect on atherosclerosis (Zhao et al, 2016), myocardial ischemia (Qin et al, 2014) and hepatic fibrosis (Wang et al, 2017). It is also benefit for emarkable function on scavenging free radicals because of its secondary metabolites, such as the well-studied active ingredient Salvianolic acids and Tashinones in the classical phytochemistry research (Roberts et al, 2007). However, the composition of Danshen vary with different regions, in order to ensuring material quality and clinical efficacy, it is urgent to look for a scientific, reliable and convenient identification method to compare the chemical composition in different regions.

Danshen has been cultivated widely in different areas (Tongchuan, Dali, Danfeng, Luonan and Shangzhou) in Shaanxi province in China. It is well known that soil, climatic, planting pattern and extraction methods can cause a change in the contents of these components in Danshen. Many methods has been researched as qualitative and/or quantitative analysis of chemical components, such as HPLC (Zhang et al, 2017), LC-MS (Liang et al, 2018), UPLC-MS (Chen et al, 2017), CE (Wang & Duan, 2014), NMR (Zhang et al, 2017), LC-DAD-MS (Hermund et al, 2018). However, it is regrettable that seldom mentioned on comparing the difference of chemical characteristics in Danshen in Shaanxi province.

In this study, with the expectations of providing a convenient quality control method for Danshen, the direct injection ESI-Q-TOF-MS technology was used to detect 18 chemical compounds present in all the samples of Danshen coming from five different locations, and most of them contain primary medicine benefits. The abundance value in MS is rather different among each composition and the same component in different locations under the same conditions. Through comprehensive analysis, there are four components can be seen as potential markers carrying on quality control in direct injection ESI-Q-TOF-MS method. The system is not only suitable for the chemical composition of Danshen in Shaanxi province, but also easily transplanted and popularized in other Danshen planting places.

1. Materials and methods

1.1 Material and Reagents

HPLC grade methanol was purchased from E. Merck, Darmstadt, Germany; Deionized water was purified by a Milli-Q system (Millipore, Bedford, MA, USA); ethanol was purchased from Shanghai Aladdin Bio-Chem Technology Co., LTD.

All the root of annual Danshen were collected from Tongchuan, Dali, Danfeng, Luonan and Shangzhou of Shaanxi province in China in September 2016.

1.2 Sample Preparation

Alcohol Extract: The roots were smashed after fully dried through a warm air (50 °C), and then sieved through a no. 60 mesh. Each of the fine powdered samples (1.0000 g) was accurately weighed and extracted with 50 mL ethanol for 30 min using microwave method. After cooling, the extracting solution was filtered through a paper filter and ethanol was removed by reduced pressure distillation. The evaporated residue was dissolved in methanol and made up to volume in a 5.0 mL volumetric flask. The solutions were filtered through a membrane filter (0.45 μm) and then injected into the ESI-Q-TOF-MS directly.

Water Extract: The roots were smashed after fully dried through a warm air (50 °C), and then sieved through a no. 60 mesh. Each of the fine powdered samples (1.0000 g) was accurately weighed and extracted with 50 mL water for 3 h in a 90 °C water bath. After cooling, the extracting solution was centrifuged at 12000 rmp for 15 min, and then removed water by freeze drying. The crude extract solution was made up in a certain concentration in water with 0.5 $mg\cdot mL^{-1}$, and filtered through a 0.45 μm membrane filter.

1.3 Instrumentation and analytical conditions

All analytes were performed on a Bruker micrOTOF-Q II ESI-Q-TOF-MS system in tune low method. Sodium formate solution was used as a calibration standard liquid in Enhanced Quadratic model. The sample injection volume was 10.0 μL and detected in tune_low method from 50 m/z to 3000 m/z. The capilary parameters were set to 4000 V for alcohol extract samples and 3500 V for water extract samples. Nebulizer pressure was set to 0.4 Bar. Carrier gas is nitrogen and helium, which has dry gas flow rate of 4.0 $L\cdot min^{-1}$ and dry heater at 180 °C.

Samples of Danshen, which were extracted from different locations in Shaanxi Province, were prepared as described before. A volume of 10.0 μL of filtered solution was injected into the instrument directly and each sample was determined parallelly three times.

1.4 Data analysis

The chromatographic data were recorded and processed with a Bruker Compass DataAnalysis 4.0 software. The ion abundance refers to the ion signal strength which was taken as the vertical coordinate in the standard apectrum. The ion abundance at the peak of ionic strength is set to be 100% in specified charge ratio, and the ratio between other ionic peak strength and the maximum peak strength is the ionic abundance at each peak.

$$A = \frac{I}{I_{\max}} \times 100\%$$

A is the ion abundance, I is the ion strength, I_{max} is the ion strength of the maximum peak .

2. Results and Discussion

ESI-Q-TOF-MS parameters such as fragmentor, spray pressure and capilary voltage which can influence the ion peak of corresponding molecular and the relative abundances were optimized for detecting to alcohol extract and water extract of Danshen. **Fig.1** is a typical direct injection ESI-Q-TOF-MS spectrum.

There were altogether 18 known chemical composition obtained from the fragment ions information which effectively reflect the structures (**Fig.2**) of Danshen composition.

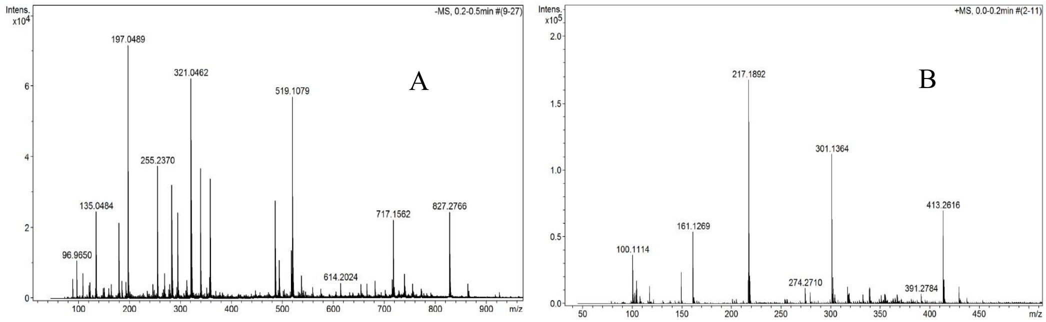

Fig.1 A typical direct injection ESI-Q-TOF-MS spectrum. A: The spectrum of the water extract of Danshen in Shangzhou; B: The spectrum of the lipid extract of Danshen in Danfeng.

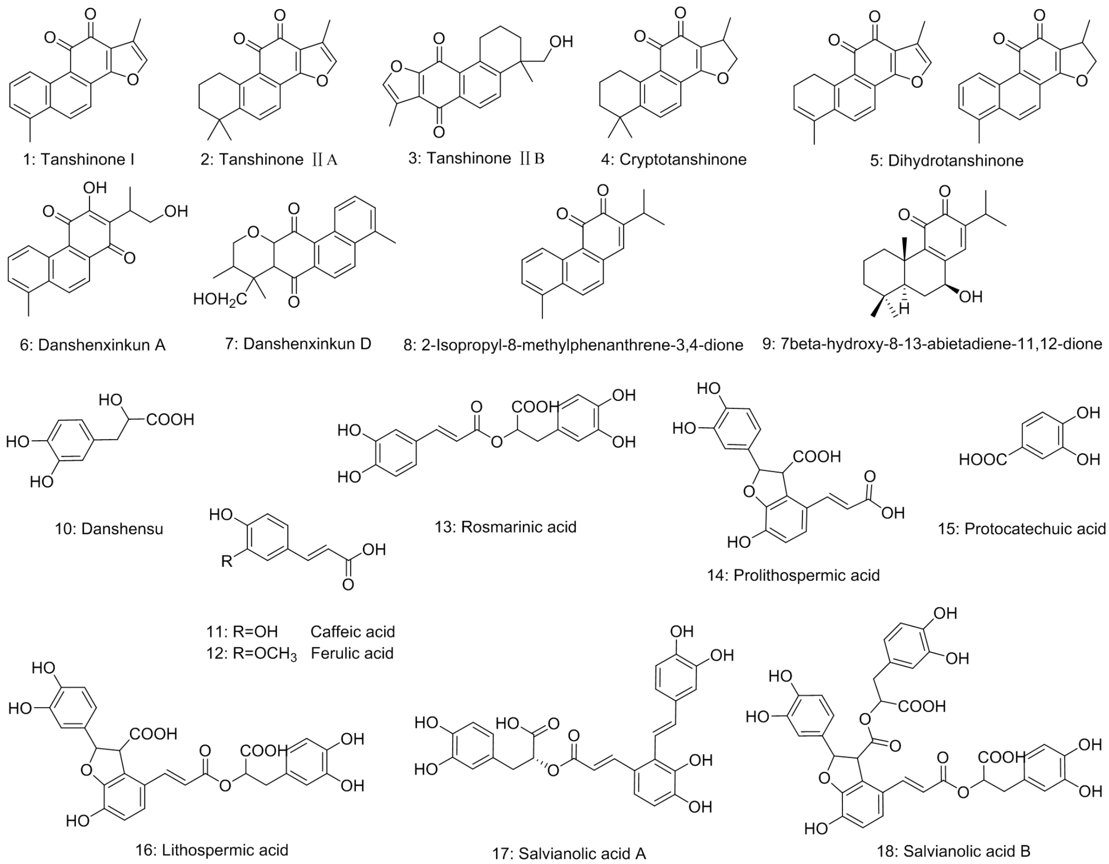

Fig.2 Chemical structures of components in Danshen detected by direct injection ESI-Q-TOF-MS

The spectrums showed concrete MS analysis results and 18 compounds were identified (Table 1). In the positive ion mode, the adduct ion of $[M+Na]^+$ was the mainly observed peaks. For instance, peak at m/z 317.1128 corresponded to the molecule of Tanshinone ⅡA with the adduct ion of $[M+Na]^+$. In the negative ion mode, the adduct ion of $[M-H]^-$ is observed as common fragment peak, for example, peak at m/z 717.1540 was the molecule of salvianolic acid B. It is nearly uniform in compounds classification among Danshen samples from five locations, but a greater distinction was existed in some specific composition.

Table 1 Identification data of chemical components of Danshen by direct injection ESI-Q-TOF-MS

Cpd.		Analyte	Calcd.(m/z)	Obsd. (m/z)
Lipophilic components	1	Tanshinone I	299.0684	299.0841 $[M+Na]^+$
	2	Tanshinone ⅡA	317.1154	317.1128 $[M+Na]^+$
	3	Tanshinone ⅡB	349.0842	349.1273 $[M+K]^+$
	4	Cryptotanshinone	301.1204	301.1277 $[M-H_2O+Na]^+$
	5	Dihydrotanshinone	279.1021	279.1558 $[M+H]^+$
	6	Danshenxinkun A	304.0712	304.2956 $[M-CH_3+Na]^+$
	7	Danshenxinkun D	332.3272	332.3273 $[M-CHO+Na]^+$
	8	2-Isopropyl-8-methylphenanthrene-3,4-dione	287.1048	287.1437 $[M+Na]^+$

	9	7-beta-hydroxy-8-13-abiet adiene-11,12-dione	302.1881	302.1415 $[M-CH_3+H]^+$
Water soluble components	10	Danshensu	197.0450	197.0487 $[M-H]^-$
	11	Caffeic acid	179.0345	179.0390 $[M-H]^-$
	12	Ferulic acid	193.0501	193.0543 $[M-H]^-$
	13	Rosmarinic acid	359.0767	359.0823 $[M-H]^-$
	14	Prolithospermic acid	339.0505	339.0563 $[M-H_2O-H]^-$
	15	Lithospermic acid	519.1033	519.1018 $[M-H_2O-H]^-$
	16	Protocatechuic acid	135.0188	135.0483 $[M-H_2O-H]^-$
	17	Salvianolic acid A	493.1135	493.1213 $[M-H]^-$
	18	Salvianolic acid B	717.1456	717.1540 $[M-H]^-$

Combined predecessor's work (Pan et al 2002), the special fragmentation of Tanshinone ⅡA as a representative lipophilic components was displayed in Fig.3. Tanshinone ⅡA lost neutral molecular fragments $-CH_3$, H_2O and -CO to form the peak at m/z 303.1237, 300.1032 and 289.1124. Fragment peak at m/z 285.1383 was obtained not only by losing a H_2O molecule from m/z 303.1237, but also via splitting a molecule $-CH_3$ from the fragment m/z 300.1032 which can split into fragment m/z 195.0441 and 272.1162. In brief, the fragmentation of Tanshinone ⅡA occurred through a loss of neutral small molecular fragments $-CH_3$, -CO, H_2O and so on.

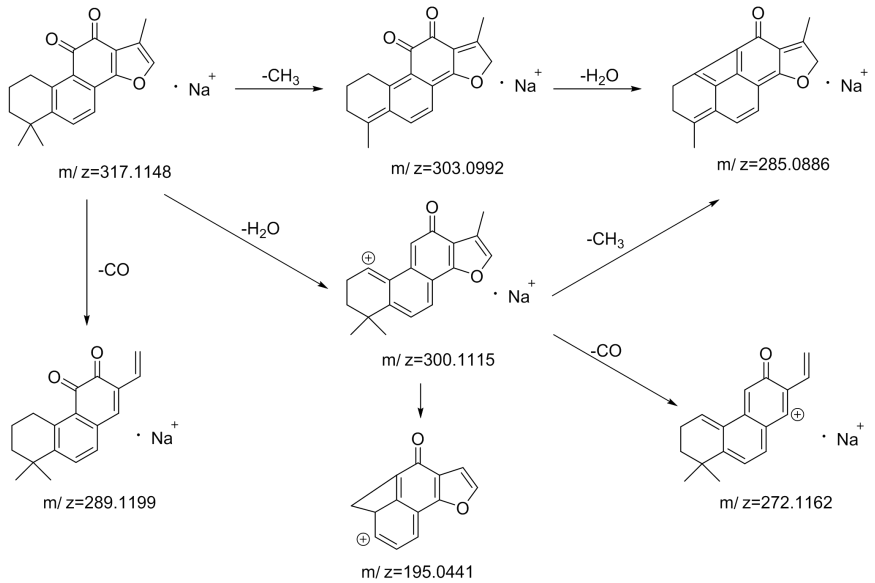

Fig.3 The fragmentation process of Tanshinone ⅡA by the adduction of $[M+Na]^+$

Through the abundance analysis, it varied quite drastically among the 18 chemical composition from five locations at the same conditions. The reason for the variation might be due to different planting environment.

For lipid solute components of Danshen from five different locations (Table 2, Fig. 4), it is obvious that the abundance of some chemical composition, such as Tanshinone I, Cryptotanshinone, Danshenxinkun A and Danshenxinkun D, varied greatly with the change of Danshen planting area. Danshen from Shangzhou had overwhelming superiority in the content of Tanshinone I, Danshenxinkun A and Danshenxinkun D with the abundance value of 72.6%, 100% and 100%. The difference gap between the maximum and the minimum value were

70.8%, 96.0% and 96.1% respectively. At the same time, Danshen from Tongchuan owned the most Cryptotanshinone with a value of 100%, followed by 63.8% in Danfeng.

Compared to the previous, other five lipid solute components don't possess big difference gap or obvious abundance degree. It is alike among the trends among Tanshinone ⅡA, Tanshinone ⅡB, Dihydrotanshinone, 2-Isopropyl-8-methylphenanthrene-3,4-dione and 7-β-hydroxy-8-13-abietadiene-11,12-dione. They respectively reached the maximum abundance value of 20.7% (Dali), 7.5% (Dali), 32.1% (Dali), 6.2% (Shangzhou) and 16.7% (Tongchuan).

In brief, the abundance value of Cryptotanshinone was the highest in all samples, the followed was Danshenxinkun A with a range from 4.0% to 100%, and other lipid solute components also owned good abundance response except Tanshinone ⅡB and 2-isopropyl-8-methylphenanthrene-3,4-dione. The rank of the content of lipid soluble components in five regions is Shangzhou > Dali >Tongchuan > Luonan >Danfeng.

Table 2 MS abundance analysis of the chemical components of Danshen in five locations

No.	Analyte	Tongchuan	Danfeng	Luonan	Dali	Shangzhou
1	Tanshinone Ⅰ	2.0%	1.8%	11.3%	9.9%	72.6%
2	Tanshinone ⅡA	13.3%	7.5%	5.5%	20.7%	9.7%
3	Tanshinone ⅡB	5.3%	2.0%	4.4%	7.5%	7.1%
4	Dihydrotanshinone	4.5%	5.0%	11.4%	32.1%	17.4%
5	Cryptotanshinone	100.0%	63.8%	34.8%	49.3%	49.5%
6	Danshenxinkun A	8.4%	4.0%	24.5%	26.4%	100.0%
7	Danshenxinkun D	8.3%	3.9%	22.4%	21.6%	100.0%
8	2-Isopropyl-8-methylphenanthrene-3,4-dione	1.6%	1.3%	5.1%	5.3%	6.2%
9	7β-hydroxy-8-13-abietadiene-11,12-dione	16.7%	11.6%	7.3%	10.3%	8.2%
10	Danshensu	100.0%	44.8%	93.5%	72.0%	100.0%
11	Caffeic acid	31.2%	13.3%	26.9%	21.7%	29.7%
12	Ferulic acid	3.4%	1.9%	1.7%	2.7%	6.6%
13	Rosmarinic acid	4.2%	1.8%	6.0%	3.9%	6.5%
14	Lithospermic acid	79.1%	58.4%	100.0%	75.3%	82.0%
15	Protocatechuic acid	33.7%	11.9%	23.3%	21.2%	34.0%
16	Prolithospermic acid	50.8%	23.0%	42.6%	36.1%	51.9%
17	Salvianolic acid A	10.3%	11.3%	11.6%	15.5%	15.9%
18	Salvianolic acid B	36.2%	56.6%	65.1%	58.4%	34.1%

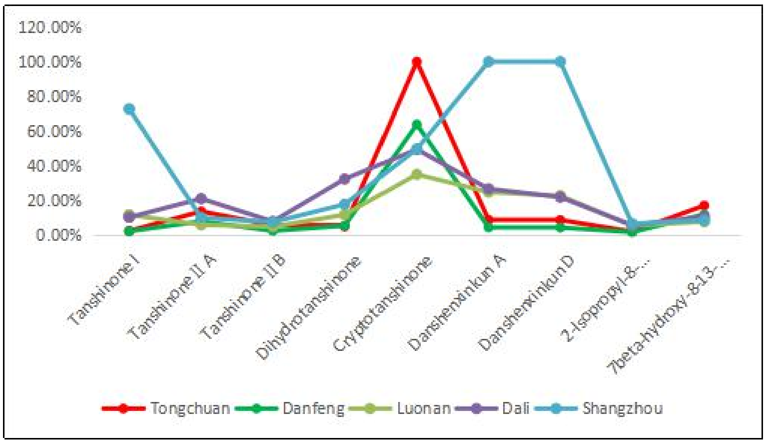

Fig.4 Abundance comparison on lipid chemical components in Danshen

For water solute components of Danshen from five different locations (Table 2, Fig.5), the tendency of abundance variation is nearly the same. All samples contain more Danshensu, Lithospermic acid, Prolithospermic acid and Salvianolic acid B than other chemical components. The four components reached the respective maximum abundance value of 100.0% (Shangzhou & Tongchuan), 100.0% (Luonan), 51.9% (Shangzhou) and 65.1% (Luonan). It was well to be reminded that Danshensu and Lithospermic acid had a higher abundance signal response with a value more than 45.0%, and abundance gap (55.2% for Danshensu, 41.6% for Lithospermic acid) was obvious from the maximum to the minimum value. In the meantime, Ferulic acid, Rosmarinic acid and Salvianolic acid A showed nearly the common variation tendency with low abundance value. They reached the maximum of 6.6%, 6.5% and 15.9% in Danshen from Shangzhou. There was no obvious distribution in different regions.

Salvianolic acid B is important as active medical component in clinic. Danshen from Luonan owned a highest abundance value of 65.1%, and the lowest level was also achieved a abundance value of 34.1% in Shangzhou.

In brief, the abundance value of Danshensu and Lithospermic acid were the highest in all samples, the followed is Salvianolic acid B with a range from 34.1% to 65.1%, and other water solute components also owned good abundance response except Ferulic acid and Rosmarinic acid. The rank of the content of water soluble components in five regions is Shangzhou > Tongchuan > Luonan > Dali > Danfeng.

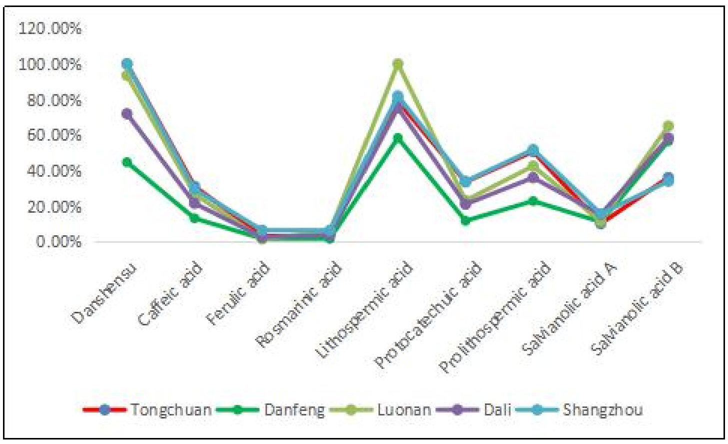

Fig.5 Abundance comparison on water chemical components in Danshen

3. Conclusion

This paper developed a scientific, reliable and convenient identification method to compare the chemical composition in Danshen from different regions by direct injection ESI-Q-TOF-MS. 18 chemical composition were identified in all Danshen samples. The chemical compunds are strongly correlated with geographical distinctions and varied quite drastically at the same conditions. By comprehensive comparison, the quality of Danshen ranked by region is Shangzhou > Tongchuan > Dali > Luonan > Danfeng. Cryptotanshinone, Danshensu, Lithospermic acid and Salvianolic acid B can help to carry on quality control as potential markers for the evaluation. Meanwhile, the method and results can be a guidance of Danshen in effective cultivation and medicinal collection in Shaanxi province.

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