

Supporting Information

TEXT 1S MEDICAL QUESTIONNAIRE

Full Name		Occupation	
Address			
E-mail Address			
Weight		Height	
Marital Status		Fertility Status	

Statement of Health

The Medical Examiner is requested to ask the following questions or to review them if they have been answered previously. Give details and dated if any of the questions below are answered with "Yes"

1. Do you currently have any health problems? Yes ☐ No ☐

2. Have you ever been hospitalized? Yes ☐ No ☐

3. Have you visited a doctor in the last three (3) years? Yes ☐ No ☐

4. Do you suffer from or have you ever suffered from any of the following

(a) Tuberculosis Yes ☐ No ☐

(b) Leprosy Yes ☐ No ☐

(c) Hepatitis (seecify type) Yes ☐ No ☐

(d) Typhoid, dysentery or any other infectious or Communicable diseases Yes ☐ No ☐

(e) AIDS or AIDS related conditions, any Immune Deficiency Syndrome Yes ☐ No ☐

(f) Genetic or Familial Disorders Yes ☐ No ☐

(g) Deafness or Chronic Ear Disease Yes ☐ No ☐

(h) Blindness or Eye Disease Yes ☐ No ☐

(i) Any cancerous disease: benign/malignant Yes ☐ No ☐

(j) Headache migraine, epilepsy or dizziness Yes ☐ No ☐

(k) Nervous or mental illness or disorders Yes ☐ No ☐

(l) Any allergies, asthma or pulmonary disease Yes ☐ No ☐

(m) Cardiovascular diseases, arterial Hypertension Yes ☐ No ☐

(n) Liver, stomach or intestinal diseases Yes ☐ No ☐

(o) Diabetes or other hormone diseases Yes ☐ No ☐

- | | | |
|--|------------------------------|-----------------------------|
| (p) Urinary tract disease | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| (q) Venereal diseases | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| (r) Rheumatism, Muscle, Joint or bone diseases | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| (s) Skin diseases | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| (t) Consmetic operations | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| (u) Any other illness or disorder | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

If “Yes” to any of the above, please give details and dates.

5. How old do you first menarche?

6. How long of your menstrual cycle?

7. What about your menstrual quality?

- ☐ Color red, without blood clot ☐ Color bleak, no congestion ☐ Color bleak, with blood clot ☐ Color red, with blood clot

8. Do you have any dysmenorrheal history? Yes ☐ No ☐

9. When do you feel pain in menstrual period?

- ☐ Before menstruation ☐ During menstruation ☐ After menstruation

10. What's duration of your dysmenorrheal?

- ☐ 1 Day ☐ 2 Days ☐ 3 Days ☐ ≥ 4 Days

11. How long do you suffer dysmenorrheal?

- ☐ 1 Year ☐ 2-3 Years ☐ 4-5 Years ☐ ≥ 6 Years

12. What type of dysmenorrhea do you think you suffered?

- ☐ Primary dysmenorrhea ☐ Secondary dysmenorrhea ☐ Uncertain

13. What do you think the reason caused dysmenorrhea?

- ☐ High pressure ☐ Nervous in menstruation ☐ Not pay attention to diet and keep warm in menstruation ☐ Genetic factors ☐ Irregular sleep ☐ Environmental factors

14. How symptoms accompany with your dysmenorrhea?

☐ Abdominal pain, distension, lumbago ☐ Nausea, vomiting and diarrhea ☐
Anxiety ☐ Breast distending pain ☐ Weak ☐ Headache or dizziness

15. What dysmenorrheal degree do you think you suffered?

☐ Mild: Not to affect the life ☐ Moderate: Affect the life ☐ Severe: Affect the life severely

16. How do you to deal with dysmenorrhea?

☐ Not to do anything, just rest ☐ Visit a doctor ☐ Take tradition Chinese medicine
☐ Take analgesics ☐ Do some exercises

The Medical Examiner is required to examine the applicant and to answer the following questions. Give details and dates if any of the questions below are answered with “Yes”.

17. **Gynecological examination**-Any signs of abnormalities? Yes ☐ No ☐

18. **B-ultrasound examination**-Any signs of abnormalities? Yes ☐ No ☐

19. **Symptoms in traditional Chinese medicine**-Any signs of Qi stagnation syndrome? Yes ☐ No ☐

20. **Comments**

Important: Please attach original results of the following

(i) Routine Blood and urine test

(ii) B-ultrasound test

Medical Examiner's Details and Declaration

Full Name and Qualifications			
Specialty		Address	
Email Address			Telephone

I hereby confirm that I have identified, questioned and examined the applicant and have answered all questions to the best of my knowledge and in good faith.

Signature of Medical Examiner

Place and Date of Examination

Name and Stamp of Medical Examiner

Table 1S. Clinical Efficacy Assessment standard of Primary Dysmenorrhea

Symptoms	Scores
Abdominal pain during the menstrual cycle or before and after menstruation	Yes 5; No 0
Obviously abdominal pain	Yes 5.5; No 0
Abdominal pain is unbearable	Yes 6; No 0
Abdominal pain is unable to sit down or sleep at ease	Yes 1; No 0
Abdominal pain effects of work and study	Yes 1; No 0
Abdominal pain and need bed rest	Yes 1; No 0
Using the general measures and relief the pain	Yes 0.5; No 0
Using the general measures and afford no relief the pain	Yes 1; No 0
Pale	Yes 0.5; No 0
Cold sweat	Yes 1; No 0
Peripheral coldness	Yes 1; No 0
Schock	Yes 2; No 0
With the waist ache	Yes 0.5; No 0
With the nausea and vomiting	Yes 0.5; No 0
With anal bulge	Yes 0.5; No 0
Pain duration add one day the score add 0.5	Yes days \times 0.5; No 0

Table 2S. UPLC - MS analytic results of Xiang-Fu-Si-Wu Formula

No.	t _R min	Ion mode	Measured Mass(<i>m/z</i>)	Calc. Mass(<i>m/z</i>)	Error (ppm)	Elemental composition	Compound	Quantit ative ions	Content (mg/g dry extract)
1	1.86	neg	169.0136	169.0137	-0.1	C ₇ H ₅ O ₅ ⁻	Gallic acid ^a	169.0	6.68
2	8.79	neg	179.0318	179.0344	-1.5	C ₉ H ₇ O ₄ ⁻	Caffeic acid ^a	179.0	1.72
3	9.72	neg	353.0812	353.0873	-1.7	C ₁₆ H ₁₇ O ₉ ⁻	Chlorogenic acid ^a	353.1	8.13
4	12.77	neg	479.1437	479.1553	-2.4	C ₂₃ H ₂₇ O ₁₁ ⁻	Albiflorin ^a	479.1	54.4
5	13.45	neg	479.1416	479.1553	-2.9	C ₂₃ H ₂₇ O ₁₁ ⁻	Peoniflorin ^a	479.1	68.7
6	16.11	neg	193.0488	193.0501	-0.7	C ₁₀ H ₉ O ₄ ⁻	Ferulaic acid ^a	193.0	6.91
7	23.78	neg	249.1477	249.1491	-0.6	C ₁₅ H ₂₁ O ₃ ⁻	Neolazppaic acid	249.1	3.22 ^b
8	30.01	neg	203.0679	203.0708	-1.4	C ₁₂ H ₁₁ O ₃ ⁻	3-butylidene-7-hydrox yphthalide	203.1	12.5 ^b
9	30.78	neg	231.1358	231.1385	-1.2	C ₁₅ H ₁₉ O ₂ ⁻	Costunolide	231.1	3.02 ^b
10	31.20	neg	255.2295	255.2324	-1.1	C ₁₆ H ₃₁ O ₂ ⁻	Palmitic acid	255.2	2.40 ^b
11	15.93	pos	342.1728	342.1705	0.7	C ₂₀ H ₂₄ NO ₄ ⁺	Tetrahydrocolumbami ne ^a	342.2	0.94
12	16.93	pos	354.1322	354.1341	-0.5	C ₂₀ H ₂₀ NO ₅ ⁺	Protopine ^a	354.1	1.63
13	17.89	pos	370.1617	370.1654	-1.0	C ₂₁ H ₂₄ NO ₅ ⁺	Allocriptopine	370.2	0.72 ^b
14	18.66	pos	324.1151	324.1236	-2.6	C ₁₉ H ₁₈ NO ₄ ⁺	Tetrahydrocoptisine ^a	324.1	0.83
15	19.17	pos	356.1862	356.1862	0	C ₂₁ H ₂₆ NO ₄ ⁺	Tetrahydropalmatine ^a	356.2	1.54
16	19.52	pos	356.1869	356.1862	0.2	C ₂₁ H ₂₆ NO ₄ ⁺	Glaucine	356.2	0.73 ^b
17	21.59	pos	370.2031	370.2018	0.4	C ₂₂ H ₂₈ NO ₄ ⁺	Corydaline ^a	370.2	7.92
18	22.17	pos	336.1205	336.1236	-0.9	C ₂₀ H ₁₈ NO ₄	Berberine ^a	336.1	0.82
19	22.87	pos	366.1655	366.1705	-1.4	C ₂₂ H ₂₄ NO ₄	Dehydrocorydaline ^a	366.2	8.64
20	28.91	pos	233.1542	233.1550	-3.4	C ₁₅ H ₂₀ NO ₂	Costuslactone	233.2	0.63 ^b

^a Confirmed by reference compounds.

^b Relative content to internal standard.

Table 3S. Precursor/product ion pairs and parameters for MRM of the marker compounds

Analyte	Retention time (min)	[M + H] ⁺ (m/z)	MRM transitions (Precursor→product)	Cone voltage (V)	Collision energy (eV)
1 Phytosphingosine	11.71	318.30	318.30→256.26	30	20
2 LysoPC (18:3)	13.67	518.33	518.33→184.07	30	20
3 LysoPC (16:1)	14.16	494.33	494.33→184.07	30	20
4 LysoPC (20:4)	14.44	544.34	544.34→184.07	30	20
5 LysoPC (18:2)	14.75	520.33	520.33→184.07	30	20
6 LysoPC (16:0) ^b	15.64	496.34	496.34→184.07	30	20
7 LysoPC (18:1)	16.05	522.36	522.36→184.07	30	20
8 Estrone ^b	9.25	271.17	271.17→147.08	30	20
9 17-Hydroxyprogesterone	11.14	331.22	331.22→138.05	30	20
10 Myristoylglycine	11.27	286.24	286.24→227.13	30	20
11 Dihydrocortisol ^b	11.78	365.23	365.23→223.10	30	20
12 Palmitoylglycine	12.78	314.27	314.27→255.16	30	20
13 Phytosphingosine	13.75	318.30	318.30→184.07	30	20
14 Sphingosine	15.15	338.24	338.24→281.23	30	20
15 LysoPC (10:0)	16.74	413.26	413.26→184.07	30	20
16 IS	9.69	748.48	748.48→158.96	30	20

Figure 1S. UPLC - ESI- MS base peak intensity (BPI) chromatograms at the positive and negative ion mode of Xiang-Fu-Si-Wu Formula

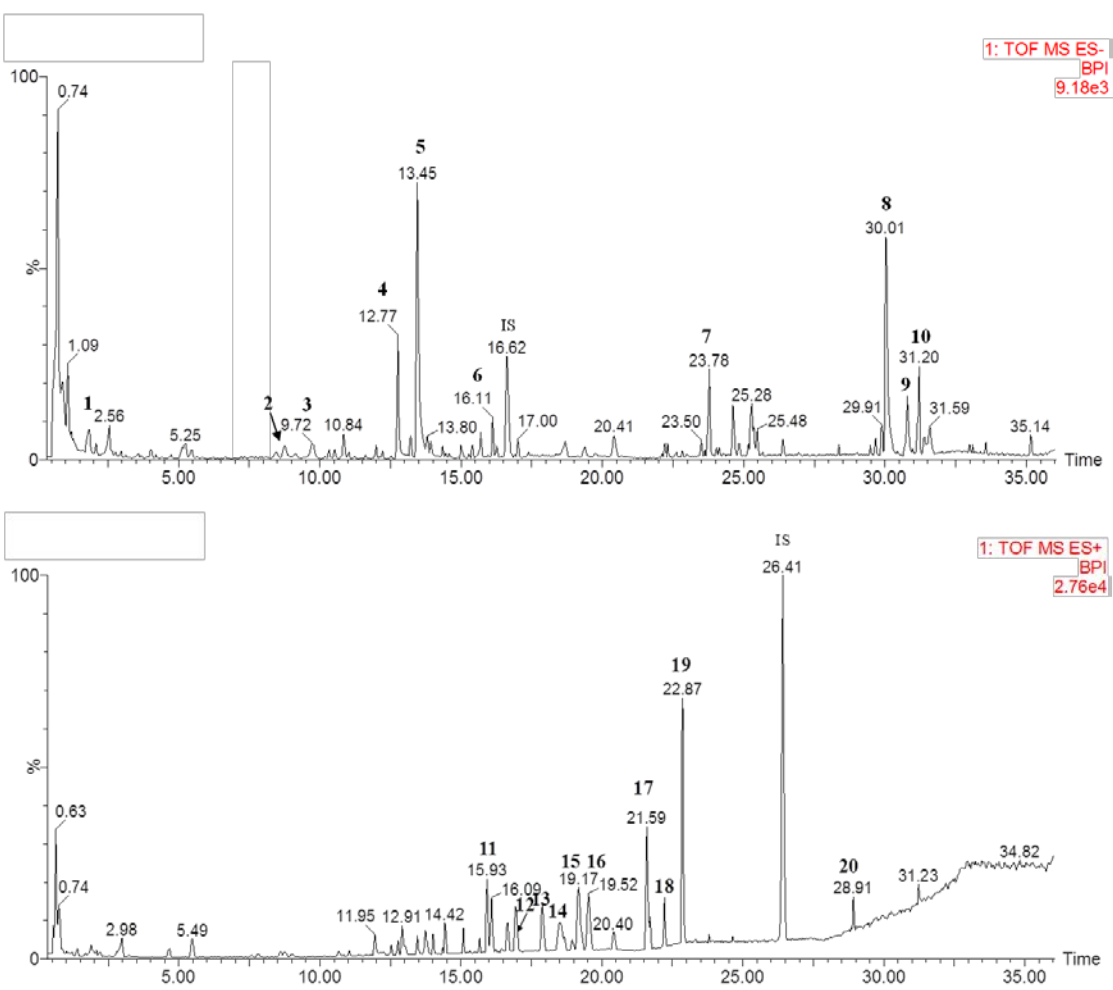
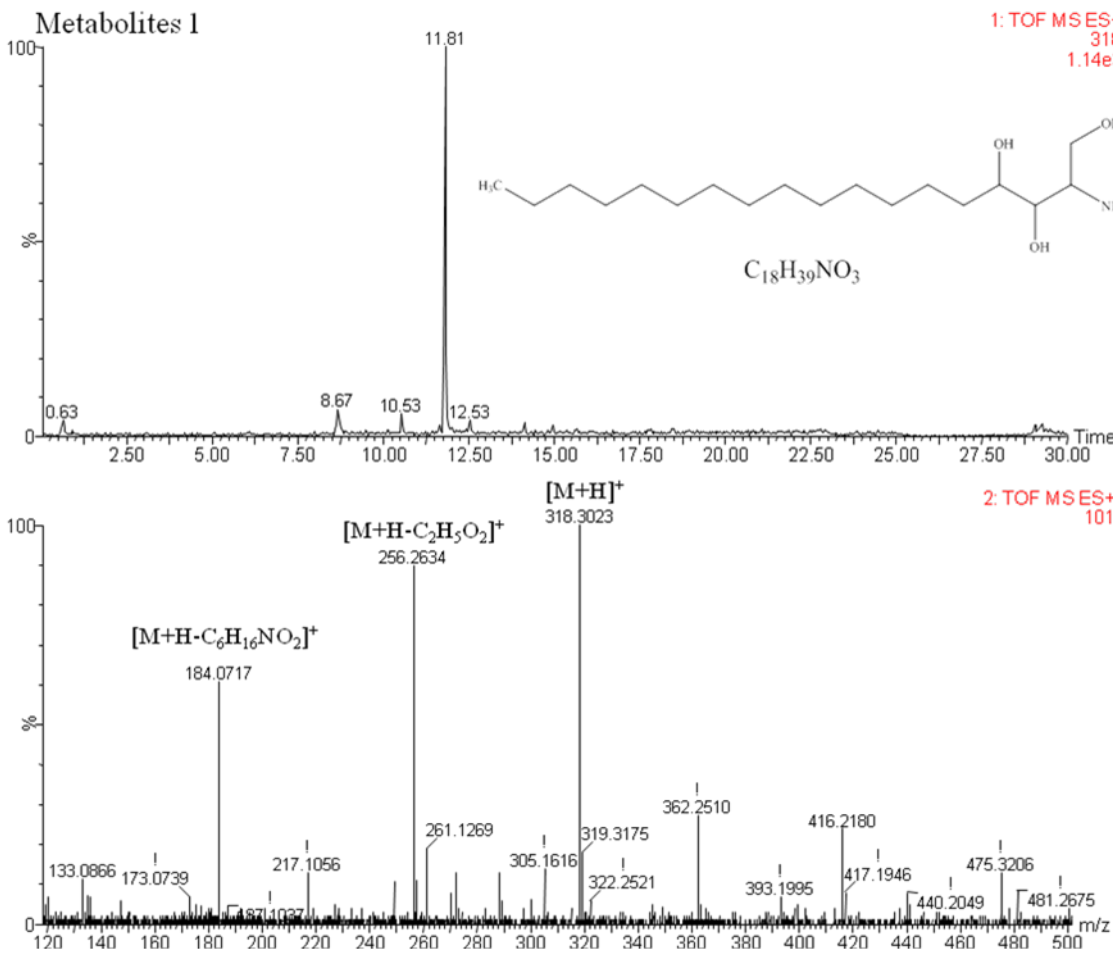
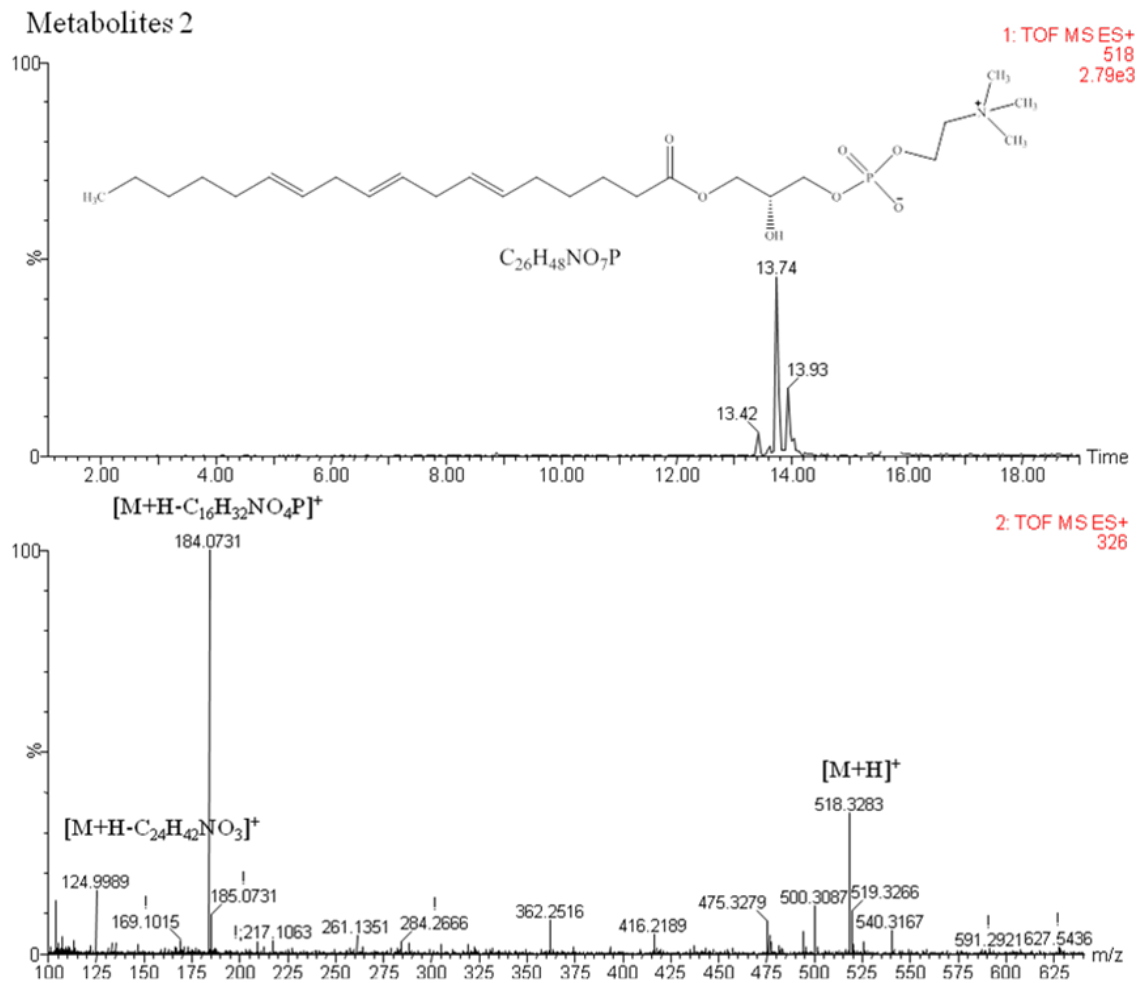
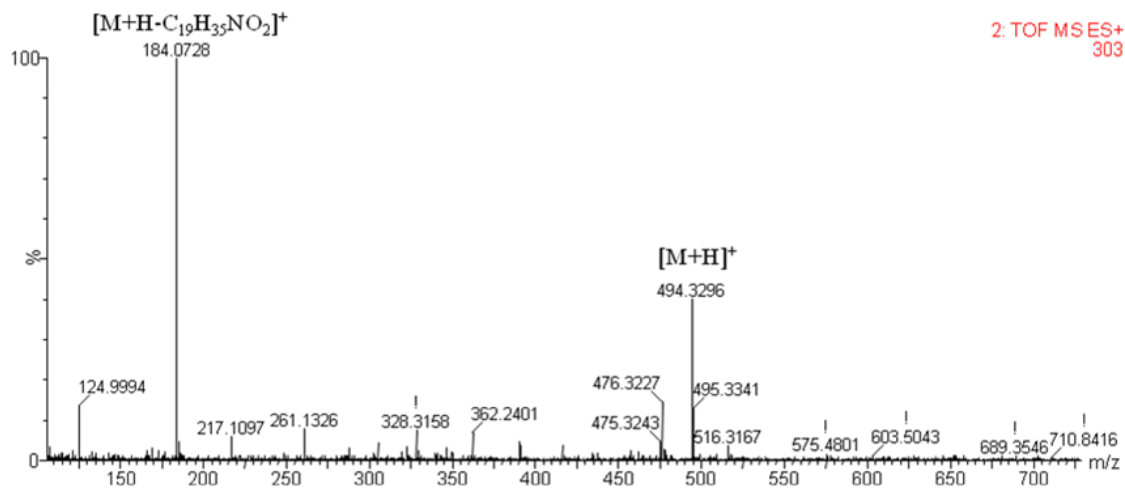
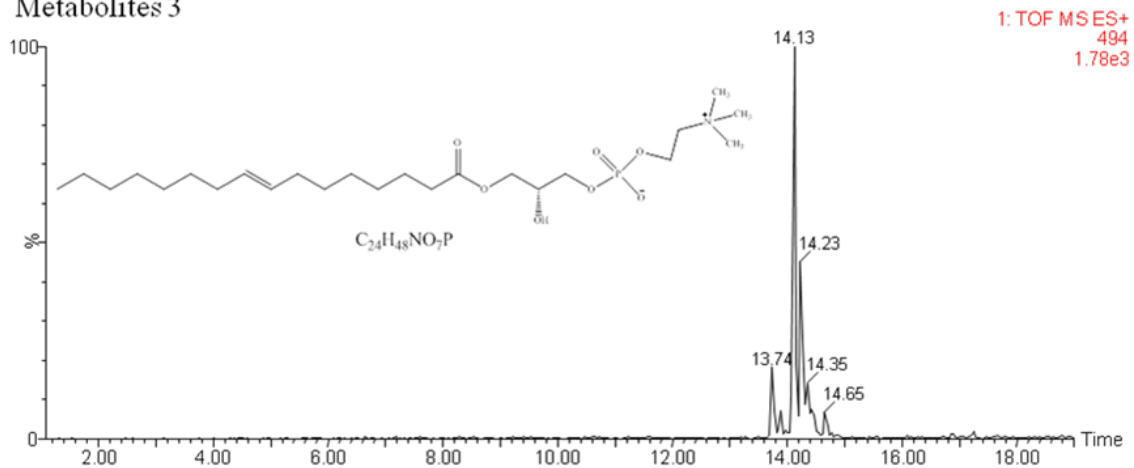


Figure 2S. Peak and corresponding mass spectrum of potential markers (Metabolites 1-15).

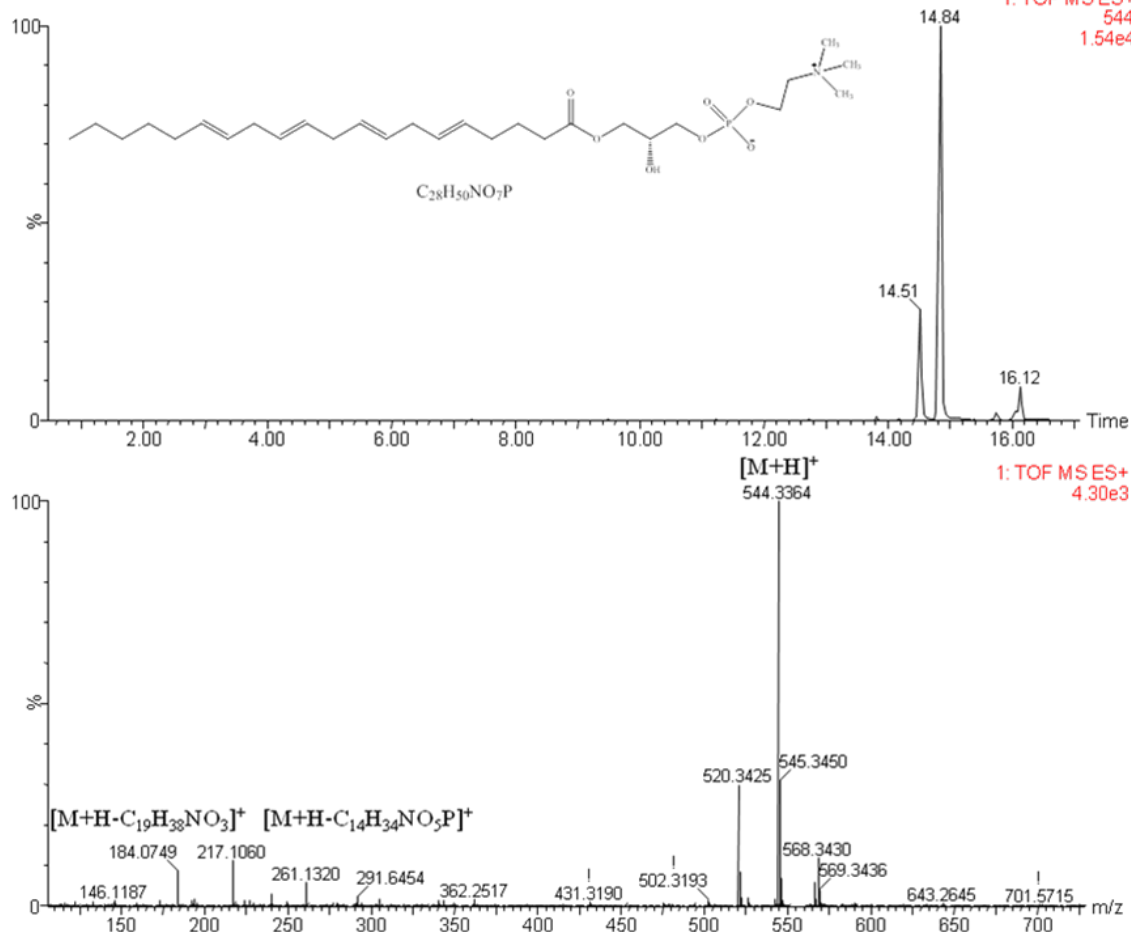




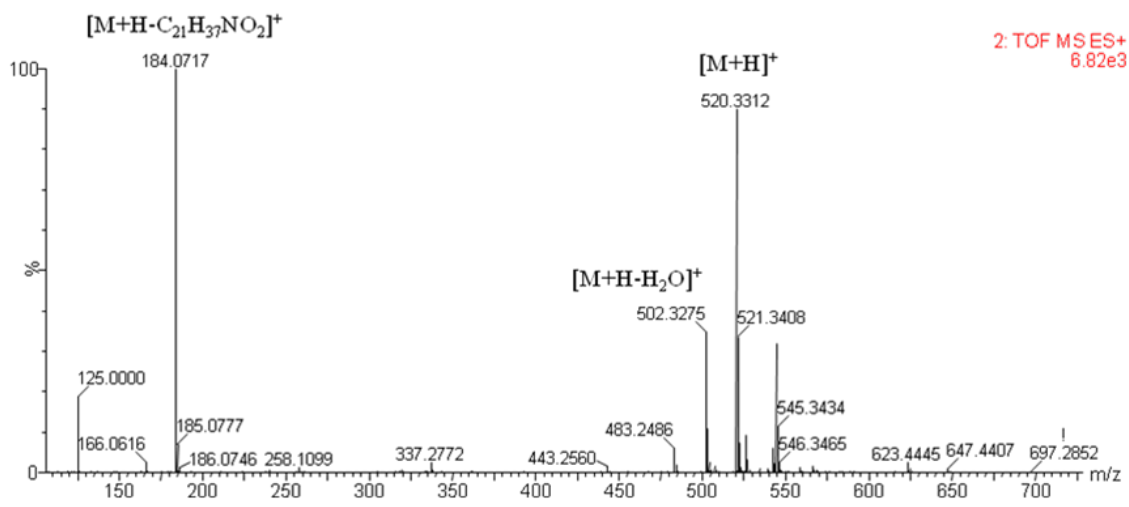
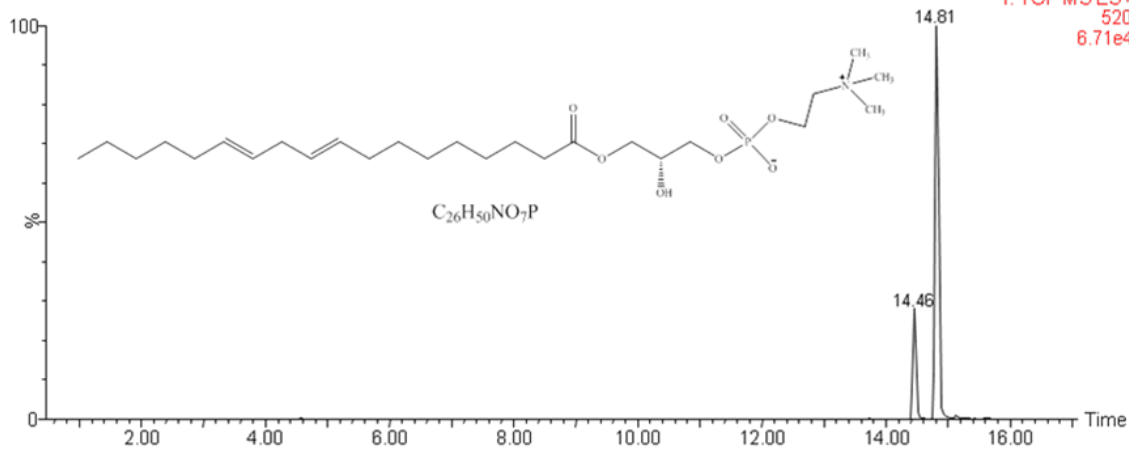
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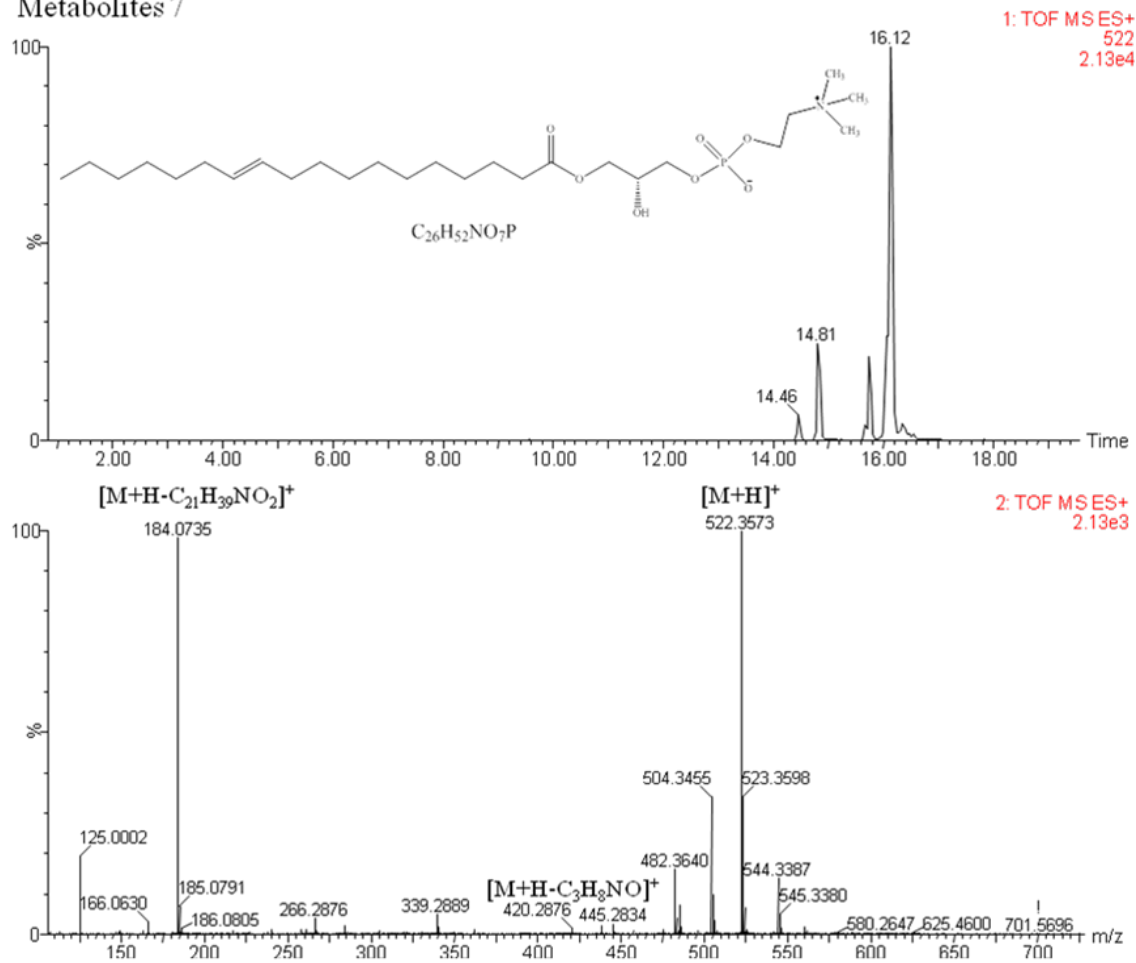
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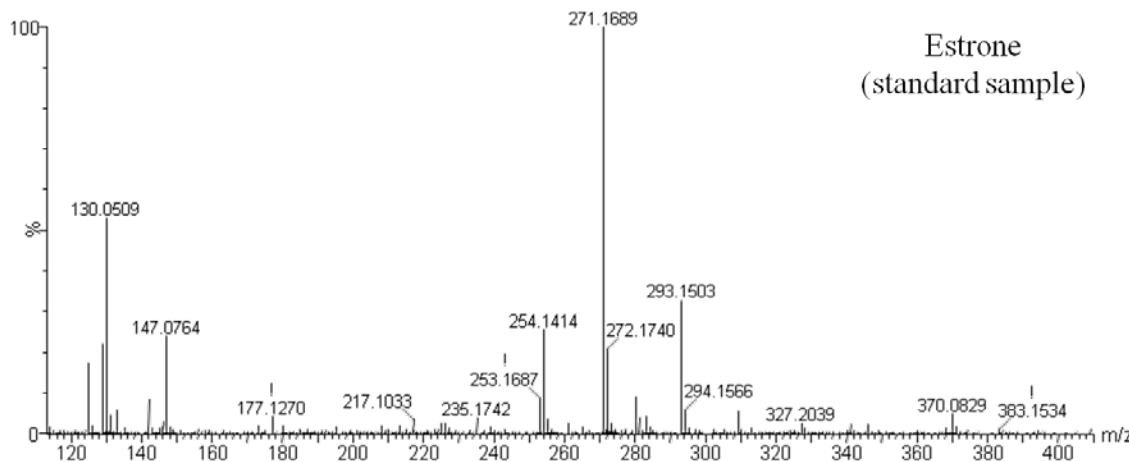
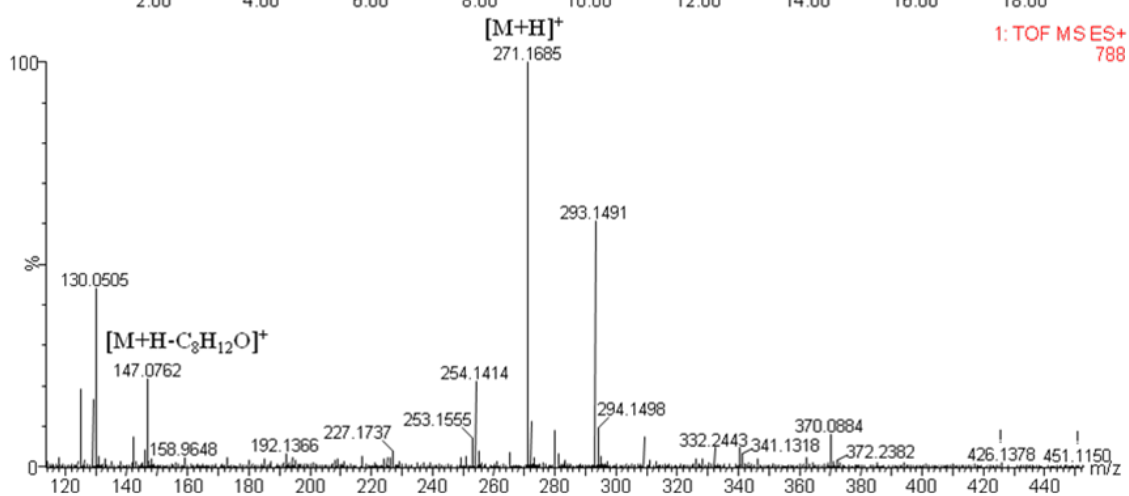
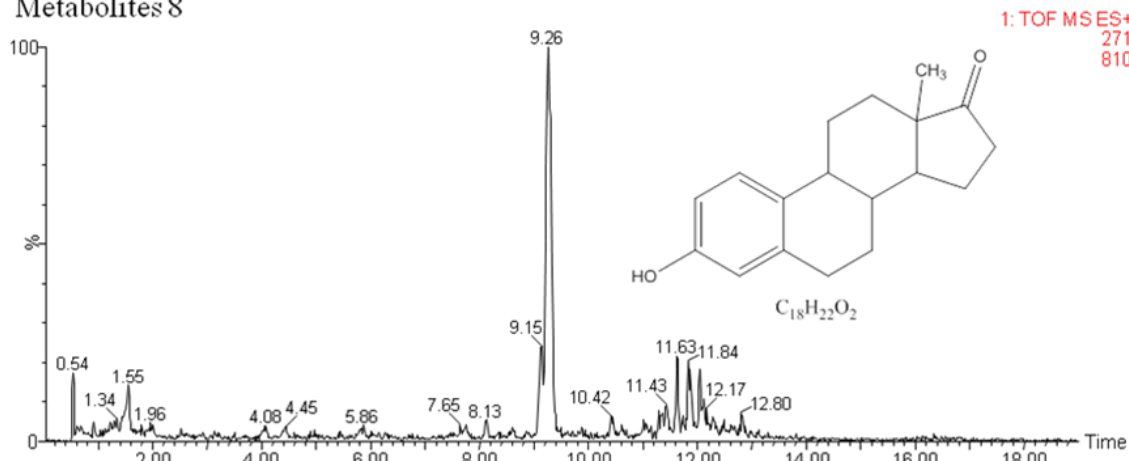
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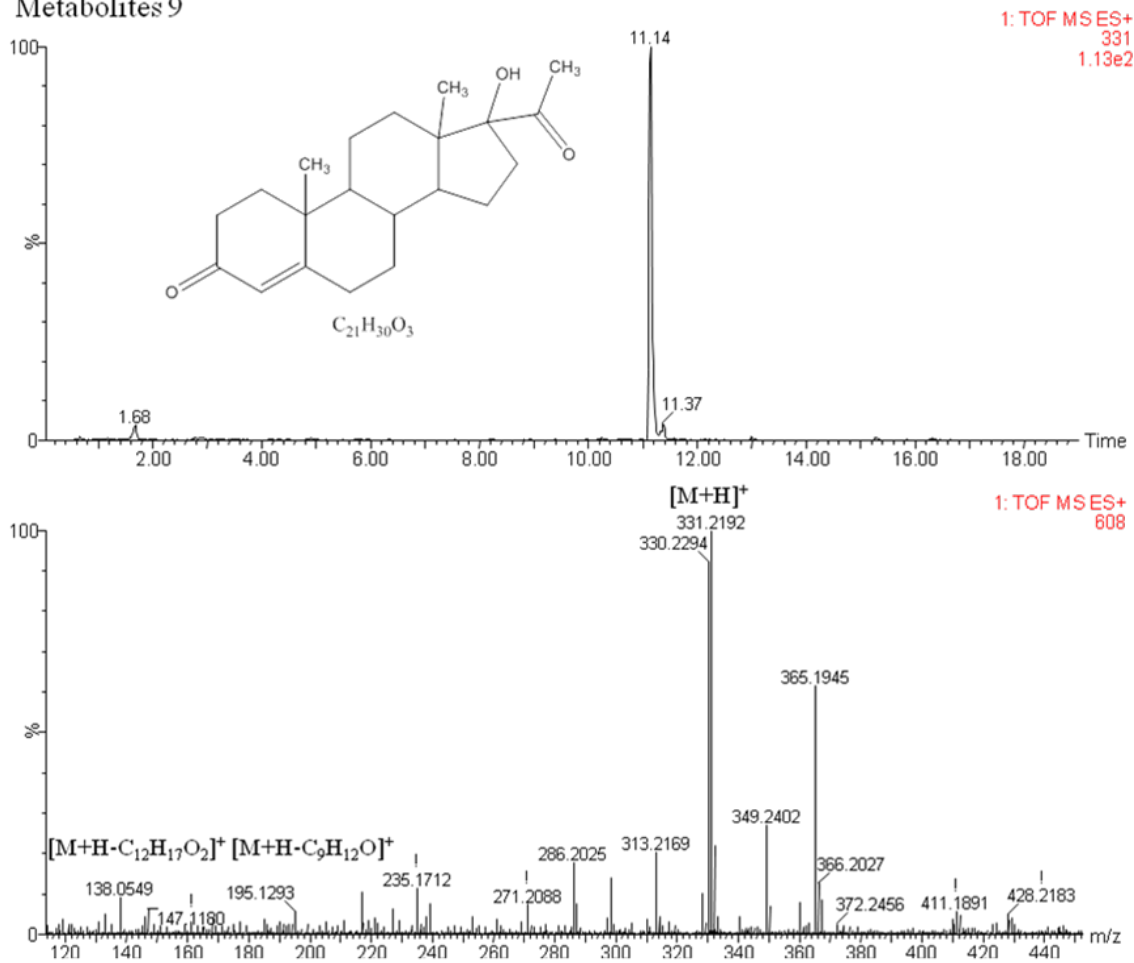
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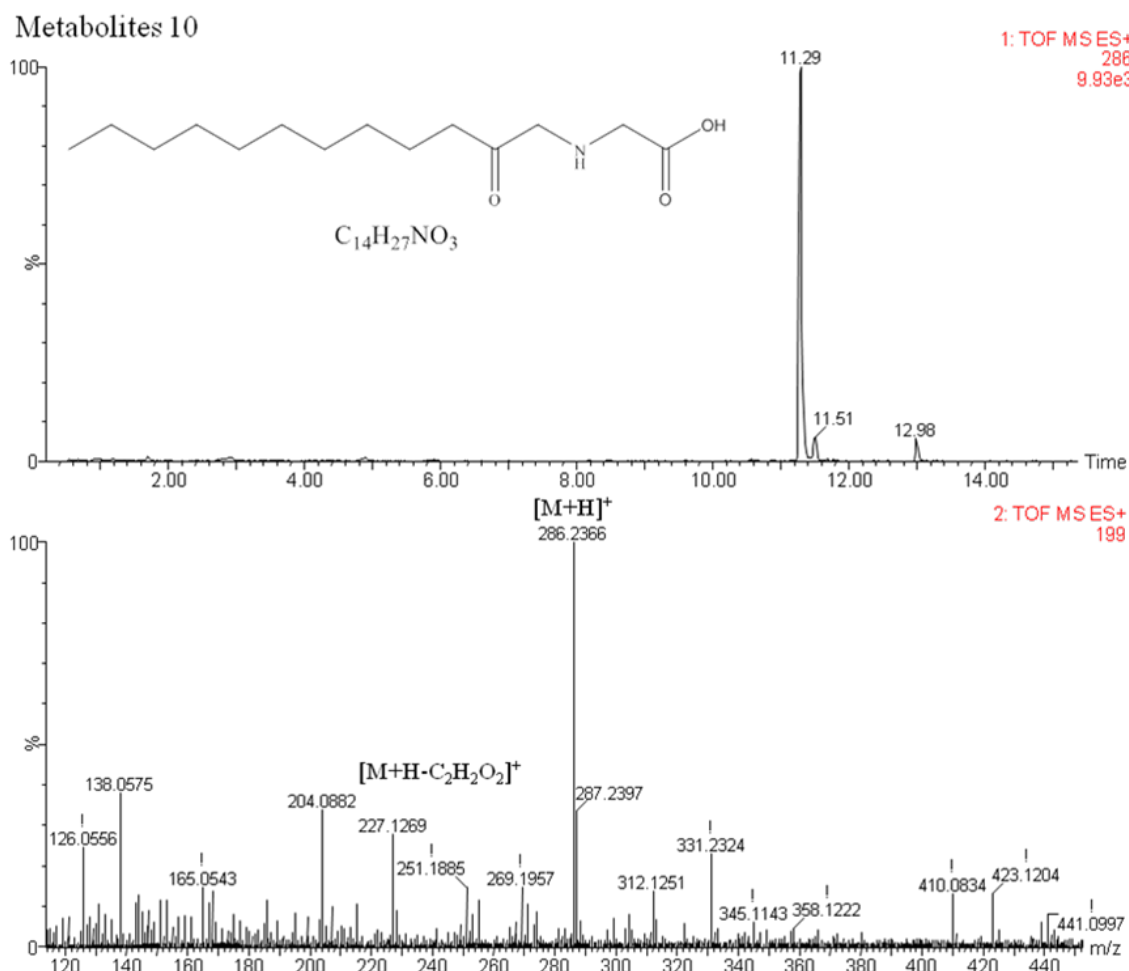


Metabolites 8

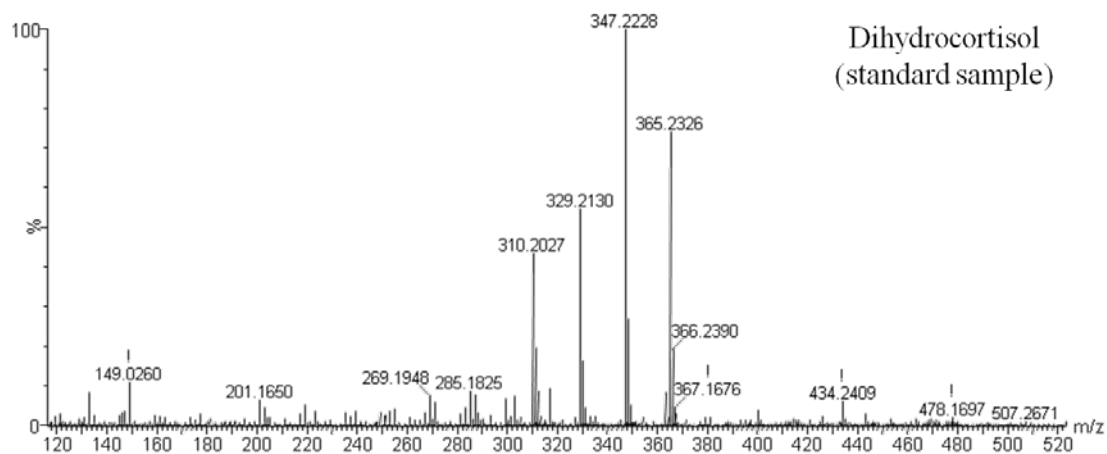
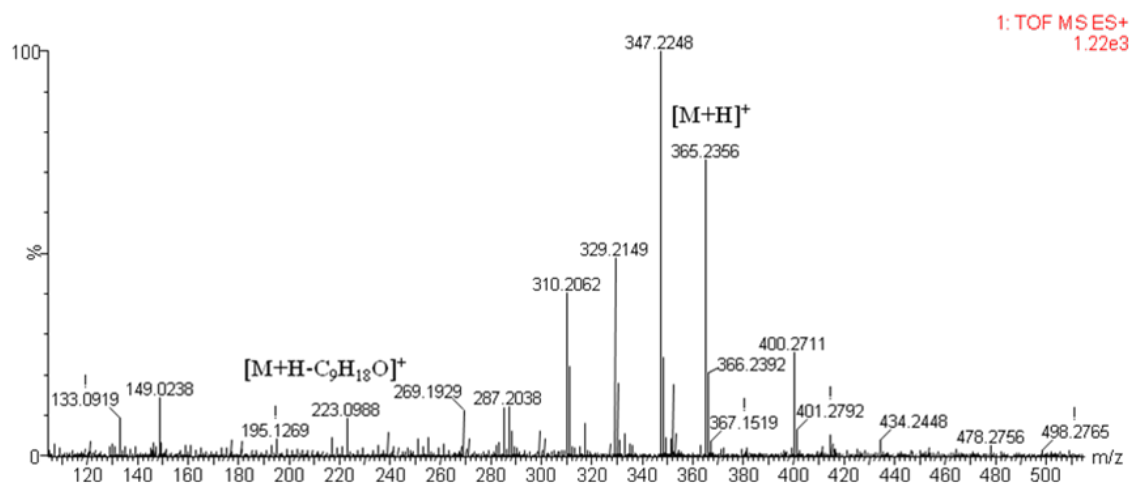
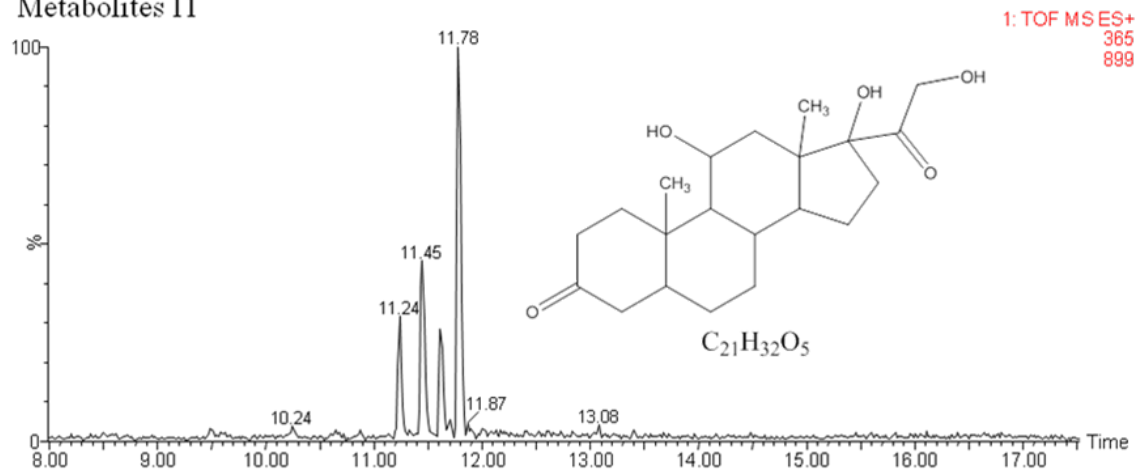


Metabolites 9

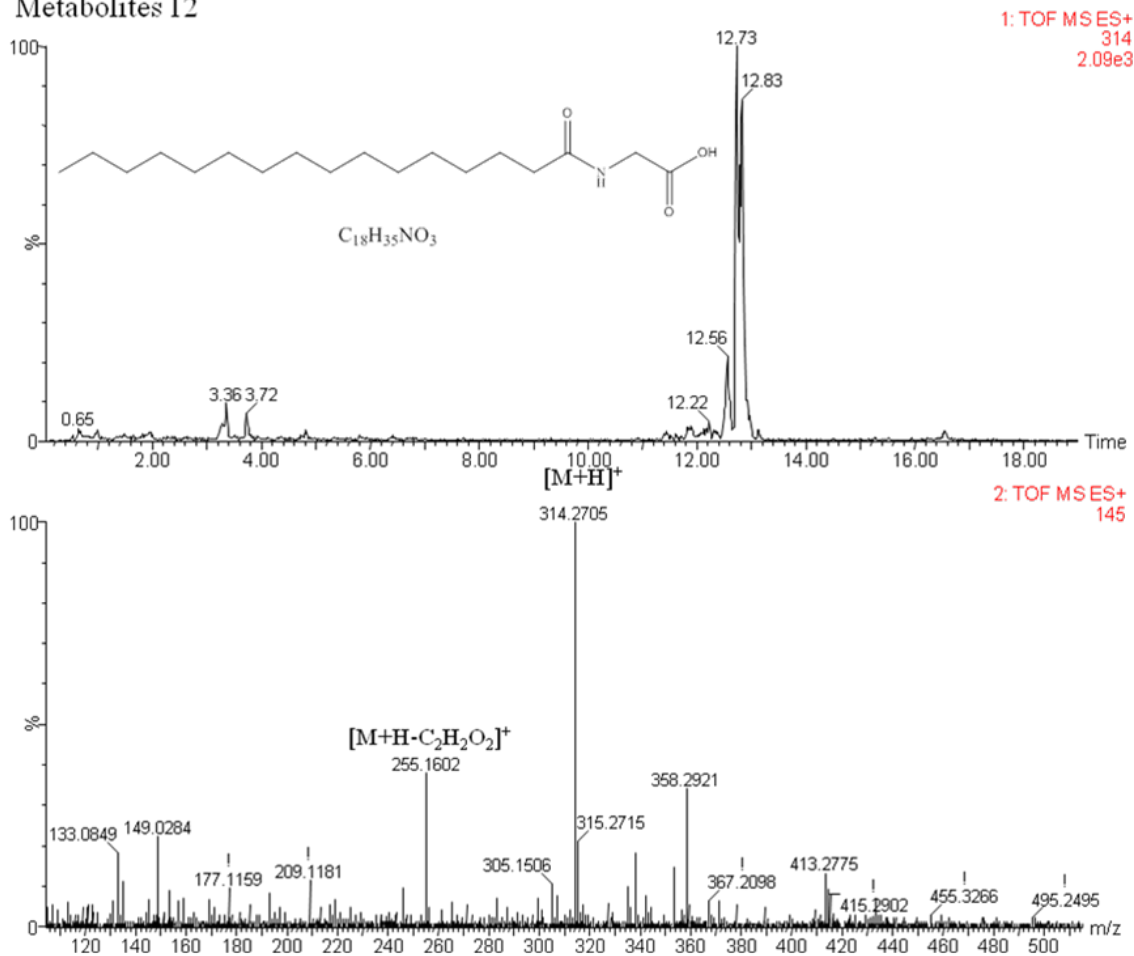




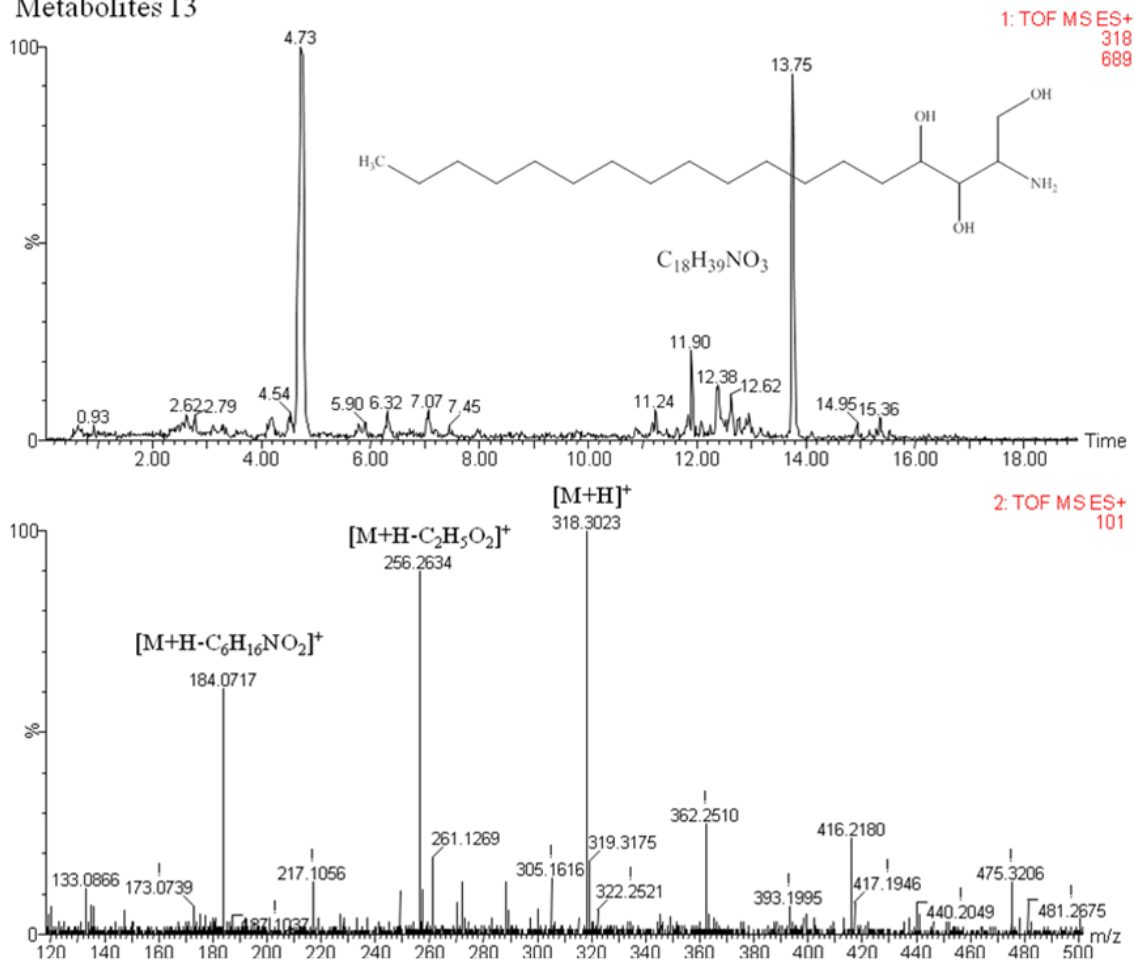
Metabolites 11



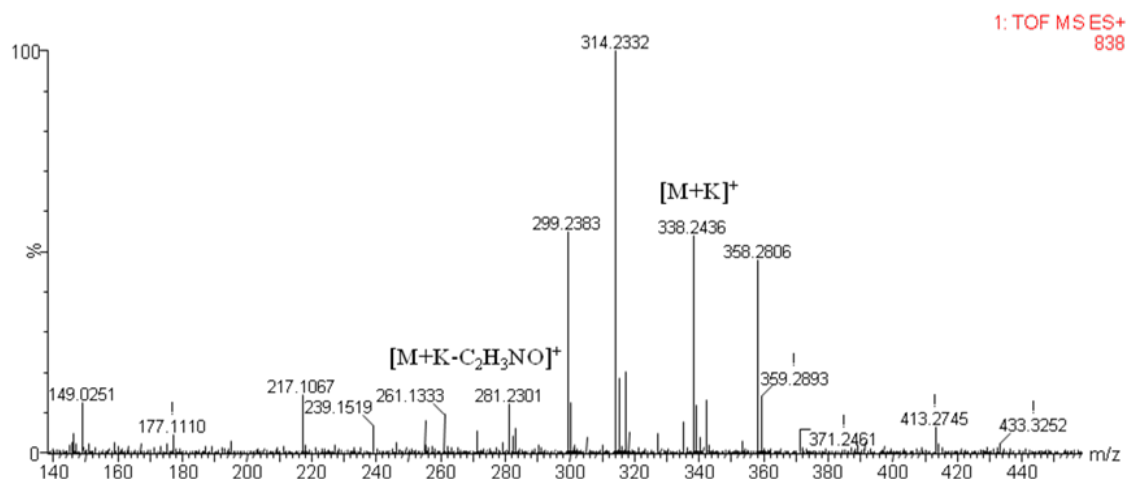
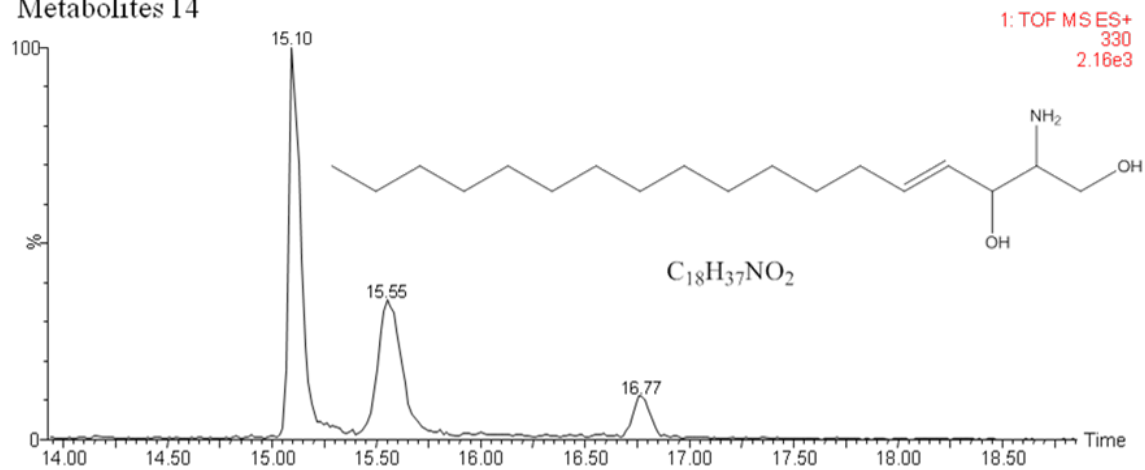
Metabolites 12



Metabolites 13



Metabolites 14



Metabolites 15

