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Secondary Metabolites Profiling of Homoeopathic Preparation of *Scrophularia Nodosa* 6C By LC-MS

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KEYWORDS

Scrophularia nodosa, Homeopathic medicine, Active components, Therapeutic potentials, Liquid chromatography

ABSTRACT:

*Scrophularia nodosa*is one of the homeopathic medicine used for the various disorders. It belongs to family Scrophulariaceae and genus Scrophularia. Various species from this genus have been used for traditional medicine. The objective of study is to determination and identification of secondary metabolites in Homoeopathic preparation of Scrophularia Nodosa 6C. In the present study, the secondary metabolite profiling was carried out using liquid chromatography coupled with mass spectroscopy. Both positive and negative modes were used for metabolite screening. Total 48 and 17 compounds were identified in positive and negative mode of LC-MS. Many active compounds from *Scrophularianodosa* are known to have therapeutic potentials. The plant is used as homoeopathic medicine. In future, the anticancer, antioxidant activity can be evaluated to check its biological activity.

1. Introduction

The use of medicinal plants emerges as an alternative to synthetic products, which are used not only in traditional medicine but also in a number of food and pharmaceutical industries, due to their nutritional properties and bioactivity (1). Higher plants produce a great variety of secondary products. Although, some of the natural products have been replaced by synthetic substitutes because of cost considerations, a number of commercially important high value chemicals are still being extracted from plants (2,3).The modern pharmaceutical industry is thus still looking for new active compounds from plant secondary metabolites (4).

*Scrophularianodosa*is one of the homeopathic medicines used for the various disorders. It belongs to family Scrophulariaceae and genus Scrophularia. More than 200 species, mostly perennials, make up the genus. The upright stems often resemble those of the Lamiaceae family because they carry lobed blooms and have square, opposite leaves. The terminal branched flowerheads with larger staminodes (non-fertile stamens) and distinctive seed casings are characteristics of Scrophularia species Various species from this genus have been used for traditional medicine. These species were *Scrophularianingpoensis*, *Scrophulariavariegate*, *Scrophularianodosa*, *Scrophulariagrossheimii*, *Scrophulariacanina*, *Scrophulariaoldhamii*, etc. *Scrophularianingpoensis*Hemsl., is extensively used for many inflammatory diseases in traditional Chinese medicine (6,7,8). It is also registered in the Chinese Pharmacopeia against febrile diseases with excessive thirst or eruptions, skin disorders, cough due to exhaustion, constipation, and conjunctivitis (9). Similar activities were reported by other species of Scrophularia such as *Scrophularia auriculata* L. or *Scrophularia canina* L. from the Mediterranean area (10,11,12).In the traditional Iranian medicine, *Scrophularia variegata* M. Bieb. And *Scrophularia striata* Boiss.were used since long time (13,14).

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In Turkish traditional medicine, *Scrophularia nodosa* L. was reported to have diuretic properties, use to treat hemorrhoids, psoriasis, pruritus, wound healing, eruptive skin diseases, and eczema (17,18). Similar activity were also reported for *Scrophularia depauperata* Boiss., *Scrophularia cryptophila* Boiss. et. Heldr. Boiss., and *Scrophularia floribunda* Boiss. et. Bal. in Turkish traditional medicine (19). *Scrophularia oldhamii* Oliv. and as a diuretic for *Scrophularia grossheimiiSchischkin* were evaluated as antipyretic and anti-inflammatory agent (15). The active components were detected by various methods from *Scrophularia* species (23). Phenylpropanoidverbascoside were detected in many species of the Scrophulariaceae family (20,21,22,23). In the present study, the secondary metabolite profiling was carried out using liquid chromatography coupled with mass spectroscopy. Both positive and negative modes were used for metabolite screening.

2. Material and Methods

2.1 Plant material collection and Extraction procedure

Ethanolic extract of *Scrophularia nodosa* were prepared for the study. The whole plant (leaf, stem, flower) was dried in the shadow and grind to form a powder. The coarse powder is prepared by method given in Homoeopathic pharmacopoeia of India volume VI.'Mother Tincture' was prepared as per the given protocol (25). Briefly, 100gm of *Scrophularia Nodosa* in coarse powder were mixed with hydroalcoholic solution (500 mlPurified Water + 537 ml Strong Alcohol). The drug strength was 1/10. The 'Mother Tincture' was diluted to form 6C concentration. A remedy labeled 6C has been diluted 1:100 six times and final dilution was 1:1,000,000,000,000.

2.2 Liquid Chromatography -Mass Spectrometry Conditions

Scrophularia nodosa extract was analyzed by liquid chromatography-mass spectrometry (LC-MS) using an Agilent Q-ToF G6540B(Agilent Technologies) connected to Agilent 1260 Infinity II HPLC.Samples (2µl) were injected onto a column Agilent Eclipse XDB-C18, 3X150 mm, 3.5 micron (Agilent) at 40°C.Chromatographic conditions for separation were as follows: The mobile phase was a combination of two solvents: 0.1% Formic acid in water(Solvent A) and0.1% Formic acid in acetonitrile (Solvent B).The flow rate was 0.3 mL/min.Chromatographic gradient conditions are given in the Table 1.

Table 1: Chromatographic gradient conditions used for separation

Time (min)	% Mobile Phase A	% Mobile Phase B
0	95	5
2	95	5
25	5	95
28	5	95
28.1	95	5
30	95	5

Dual AJS ESIwas used as MS ion source.The components were subjected to the mass analyzer through electrospray ionization probe operating in positive and negative mode with the following conditions: nebulizer gas temp300°C; sheath gas temp and gas flow was 350 °C and 11 l/min, respectively; capillary voltage 3500 V; nebulizer gas: 35 psig; drying gas: 8 l/min; sheath: 11 l/min and nozzle voltage: 1000 V.MS scan range was at m/z 100 to 1700. Masshunter workstation software v. B.05.01 was used for this analysis.

3. Results

The *Scrophularia nodosa* (6C) extract was evaluated for its secondary metabolites by LC-MS.

3.1 Compounds detected by positive mode of LC-MS

Table 1 shows the secondary metabolites detected at positive mode of LC-MS. Around 143 compounds were detected. Out of which 48 compounds were identified. Those compounds were given in Table 2. These compounds were detected between retention time 2.115 to 29.083 and the mass of compounds were ranges between 118.0784 and 743.5460.

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Table 2: List of compounds detected by the positive mode of LC-MS

Sr. No.	Compound name	Structural formula	RT	Mass
1	Boviquinone 4	C26 H36 O4	2.115	412.2606
2	Lathyrine	C7 H10 N4 O2	2.139	182.0802
3	3-b-Galactopyranosylglucose	C12 H22 O11	2.230	342.1177
4	Nicotinamide N-oxide	C6 H6 N2 O2	2.432	138.0434
5	3-Butylpyridine	C9 H13 N	2.507	135.1051
6	2-Methoxybenzenethiol	C7 H8 O S	3.008	140.0297
7	Funtumine	C21 H35 N O	11.463	317.2724
8	Istamycin	C1 C19 H37 N5 O6	11.625	431.2750
9	Netilmicin	C21 H41 N5 O7	11.962	475.3012
10	Tamsulosin	C20 H28 N2 O5 S	14.599	408.1738
11	2-Methyl-4-pentyloxazole	C9 H15 N O	15.373	153.1161
12	Histidinyl-Phenylalanine	C15 H18 N4 O3	16.832	302.1383
13	Phenylalanyl-Histidine	C15 H18 N4 O3	16.836	302.1380
14	Duloxetine	C18 H19 N O S	17.366	297.1201
15	2-Methylundecanal	C12 H24 O	17.496	184.1836
16	(Z)-6-Nonenal	C9 H16 O	19.755	140.1208
17	C16 Sphinganine	C16 H35 N O2	20.021	273.2680
18	Anapheline	C13 H24 N2 O	20.096	224. 1898
19	2-Pentadecanone	C15 H30 O	20.869	226.2306
20	2-Hexadecanone	C16 H32 O	21.526	240.2461
21	Erysopine	C17 H19 N O3	21.552	285.1377
22	Cyclocalopin F	C15 H18 O6	22.109	294.1117
23	9-alpha-Fluoro-11beta,16alpha,17alpha,21-tetrahydroxypregn-4-ene-3,20-dione	C21 H29 F O6	22.109	396.1952
24	alpha-Methylstyrene	C9 H10	22.109	118.0784
25	3'-Hydroxy-HT2 toxin	C22 H32 O9	22.110	440.2027
26	Militarinone A	C26 H37 N O6	22.110	459.2637
27	(24E)-3alpha-Acetoxy-15alpha-hydroxy-23-oxo-7,9(11),24-lanostatrien-26-oic acid	C32 H46 O6	22.110	526.3311
28	Withanolide A	C28 H38 O6	22.110	470.2684
29	Lucidenolactone	C27 H36 O6	22.111	456.2528
30	Armillaripin	C24 H30 O6	22.112	414.2059
31	Armillaripin	C24 H30 O6	23.048	414.2058
32	C14:1n-9	C14 H26 O2	23.233	226.1942
33	Austalide L	C25 H32 O6	23.496	428.2213
34	Armillaripin	C24 H30 O6	24.137	414.2057
35	1,11-Undecanedicarboxylicacid	C13 H24 O4	24.542	244.1685
36	9-Fluoro-16alphahydroxyandrost-4-ene-3,11,17-trione	C19 H23 F O4	25.410	334.1587
37	Oleyl alcohol	C18 H36 O	25.963	268.2776
38	Austrobailignan7	C20 H22 O5	26.062	342.1478
39	Kanzonol R	C22 H26 O5	26.090	370.1794
40	(6beta,7alpha,12beta,13 beta)-7-Hydroxy-11,16-dioxo-8,14-apianadien- 22,6-olide	C23 H28 O5	26.098	384.1950
41	Austrobailignan 7	C20 H22 O5	26.175	342.1482
42	9alpha-Fluoro- 11beta,16alpha,17alpha, 21-tetrahydroxypregn-4-ene-3,20-dione	C21 H29 F O6	26.545	396.1953
43	9alpha–Fluoro-11beta,16alpha, 17 alpha, 21-tetrahydroxypregn-4-ene-3,20-dione	C21 H29 F O6	26.964	396.1949
44	PE(14:0/22:2(13Z,16Z))	C41 H78 N O8 P	27.488	743.5460

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45	Monoisobutylphthalicacid	C12 H14 O4	27.988	222.0902
46	Capsi-amide	C17 H35 N O	28.178	269.2728
47	Cinitapride	C21 H30 N4 O4	28.396	402.2273
48	Corrinoid	C19 H22 N4	29.083	306.1845

Figure 1 and 2 showed the compound chromatograms and spectra of compounds 1-12 along with its structures, respectively.

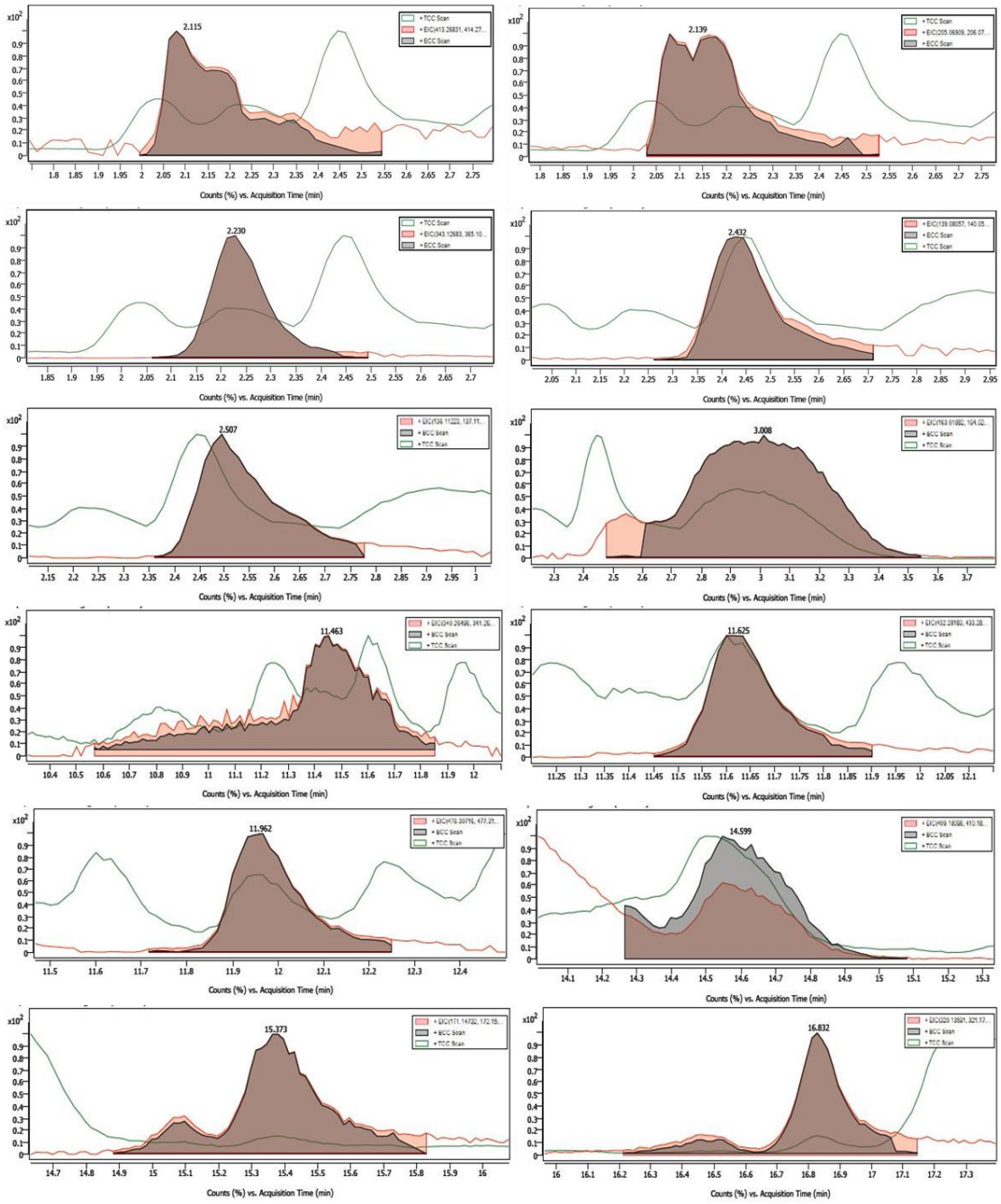

Figure 1: Compound chromatograms of secondary metabolites detected by positive mode of LC-MS (Compound number 1-12 from Table 2)

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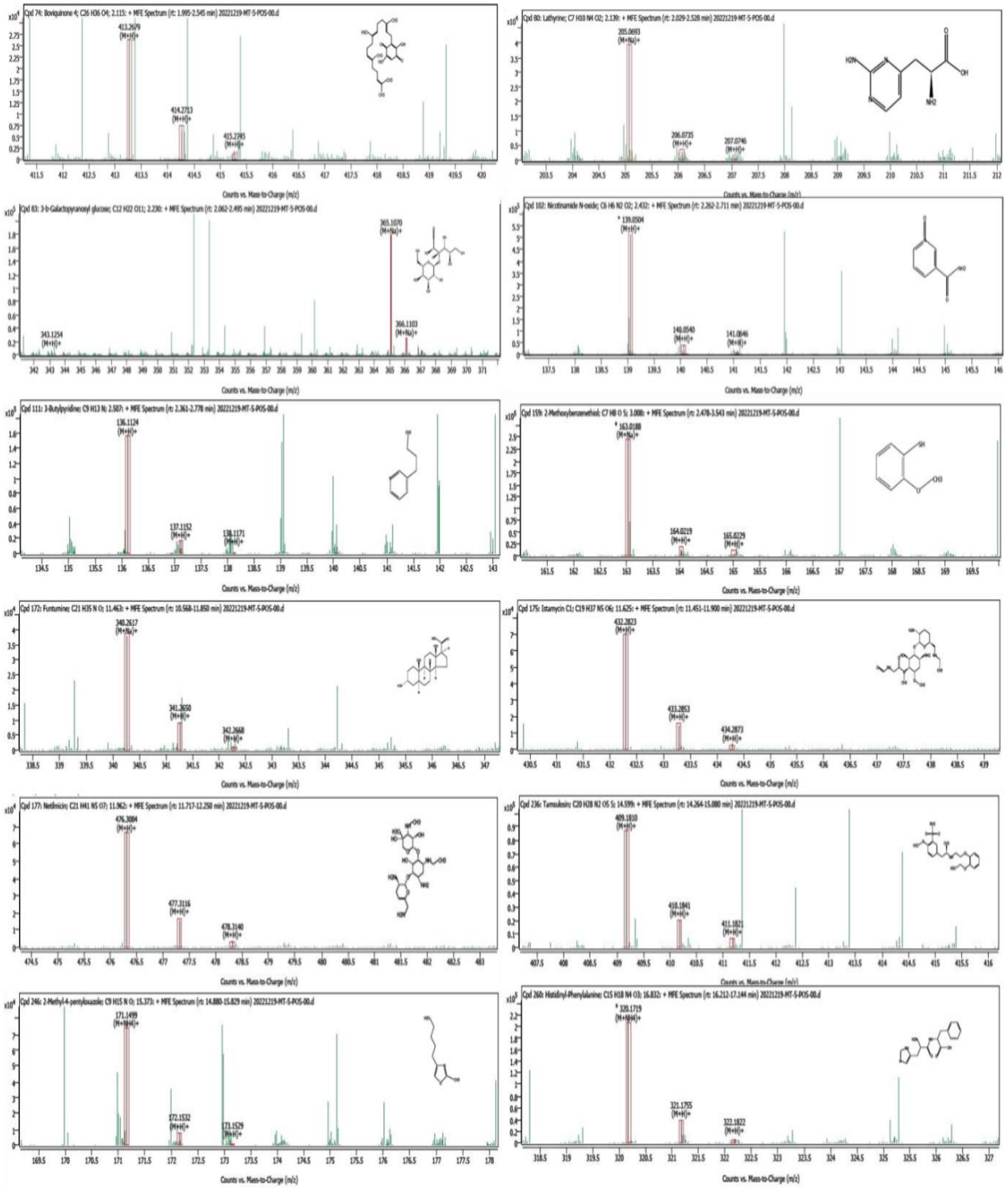

Figure 2: Compound spectra along with its structures of secondary metabolites detected by positive mode of LC-MS (Compound number 1-12 from Table 2)

Figure 3 and 4 showed the compound chromatograms and spectra of compounds 13-24(from Table 2) along with its structures, respectively.

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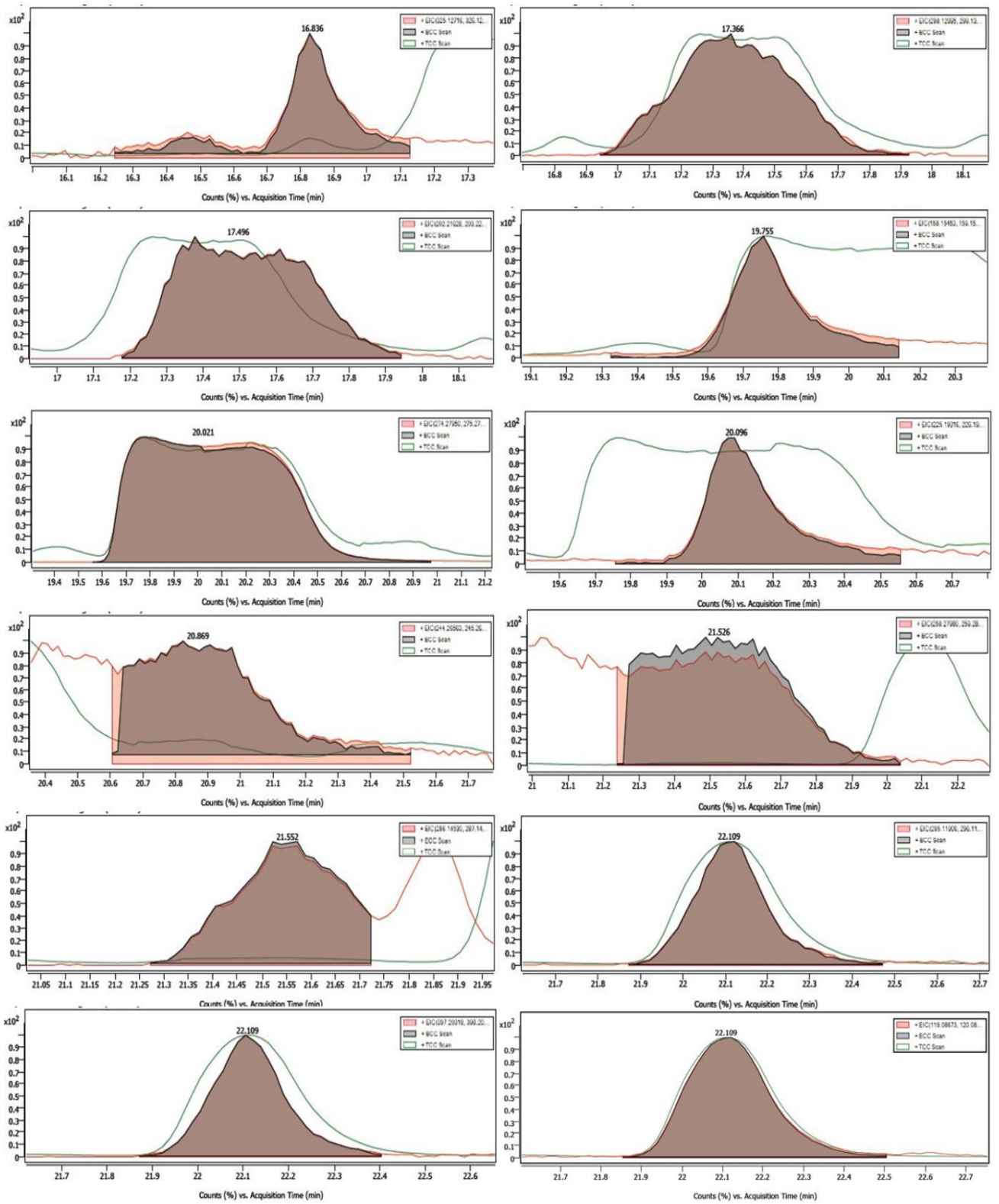

Figure 3: Compound chromatograms of secondary metabolites detected by positive mode of LC-MS (Compound number 13- 24 from Table 2)

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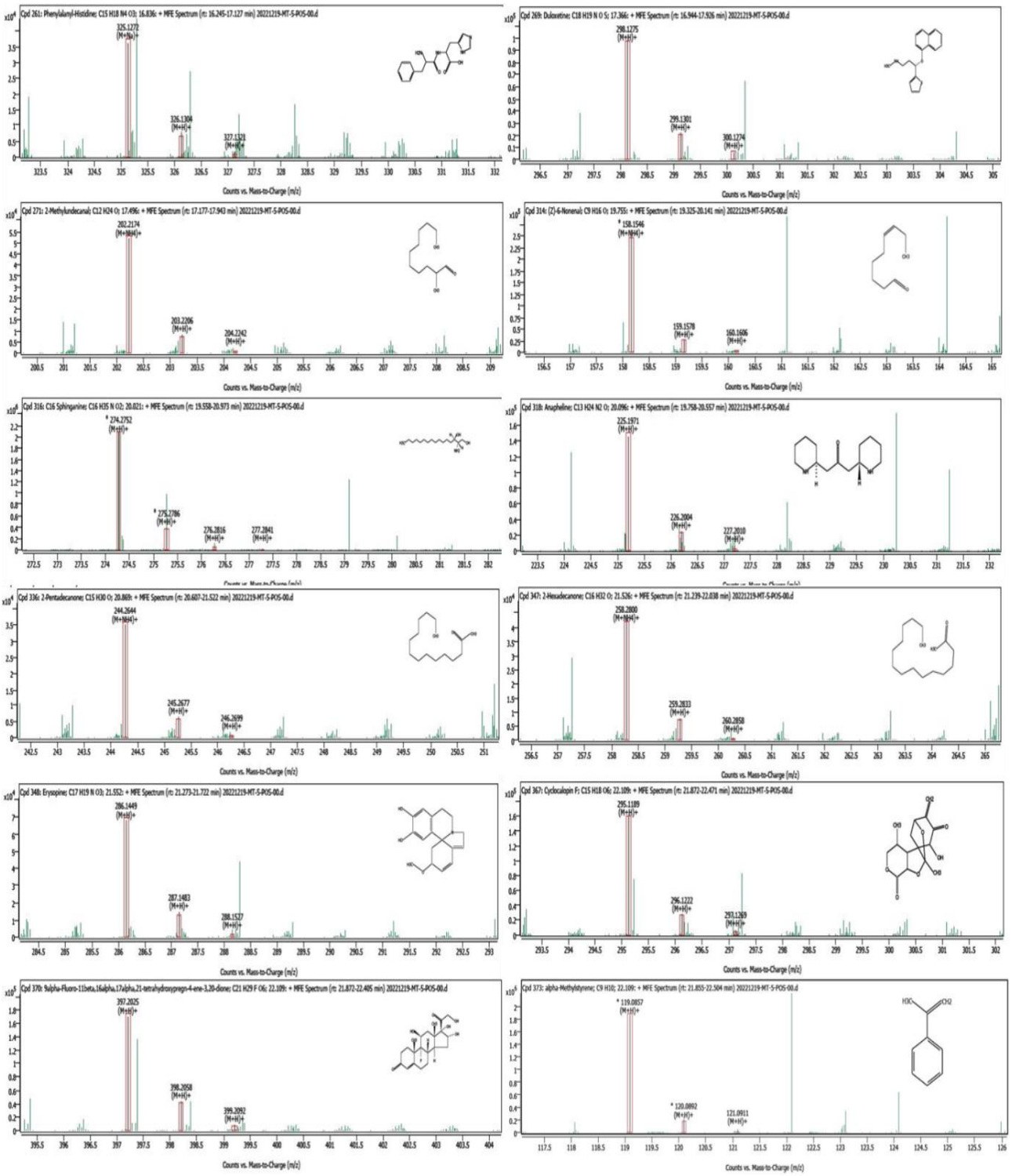

Figure 4: Compound spectra along with its structures of secondary metabolites detected by positive mode of LC-MS (Compound number 13- 24 from Table 2)

Figure 5 and 6 showed the compound chromatograms and spectra of compounds 25-36 (from Table 2) along with its structures, respectively.

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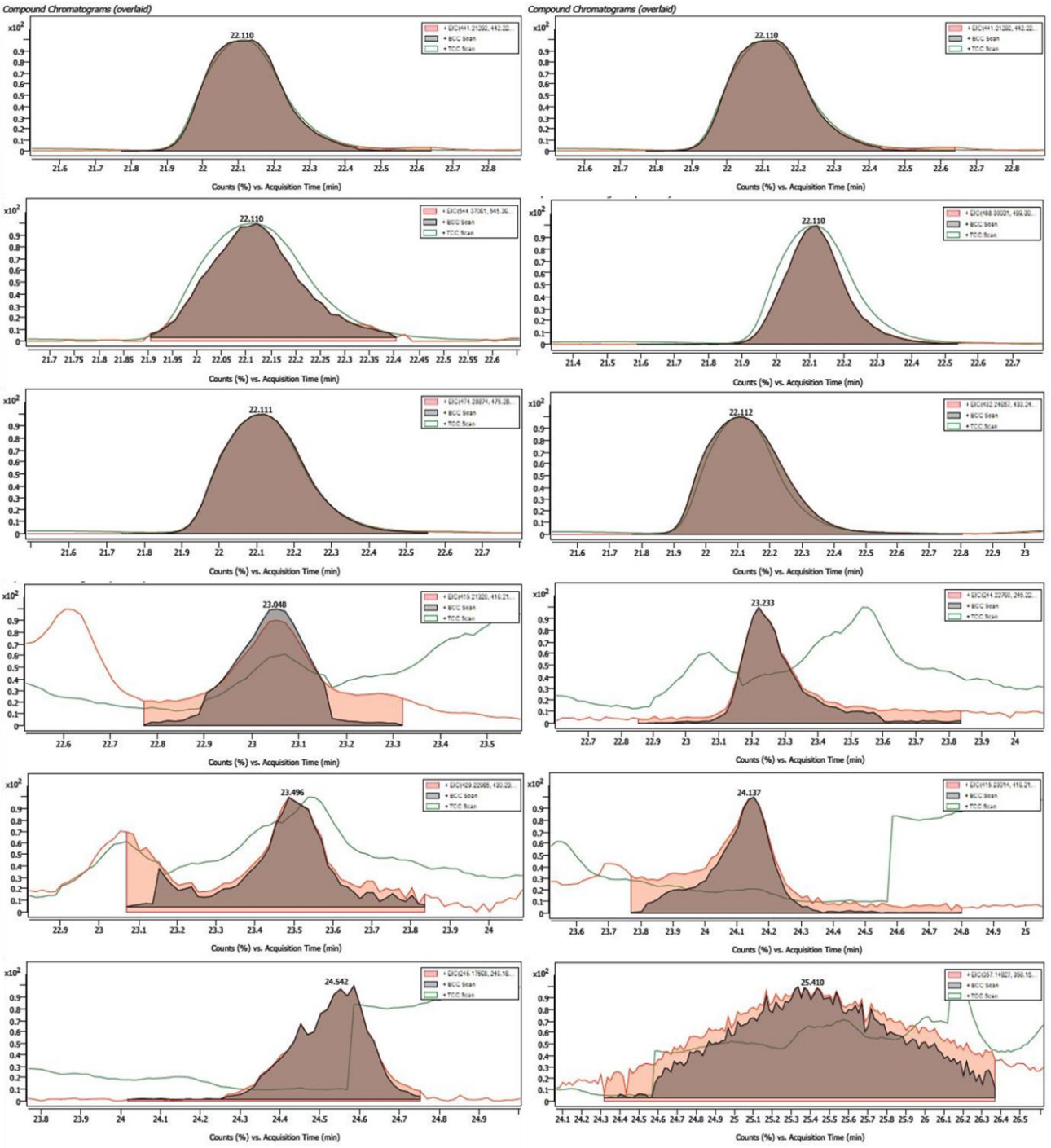

Figure 5: Compound chromatograms of secondary metabolites detected by positive mode of LC-MS (Compound number 25- 36 from Table 2)

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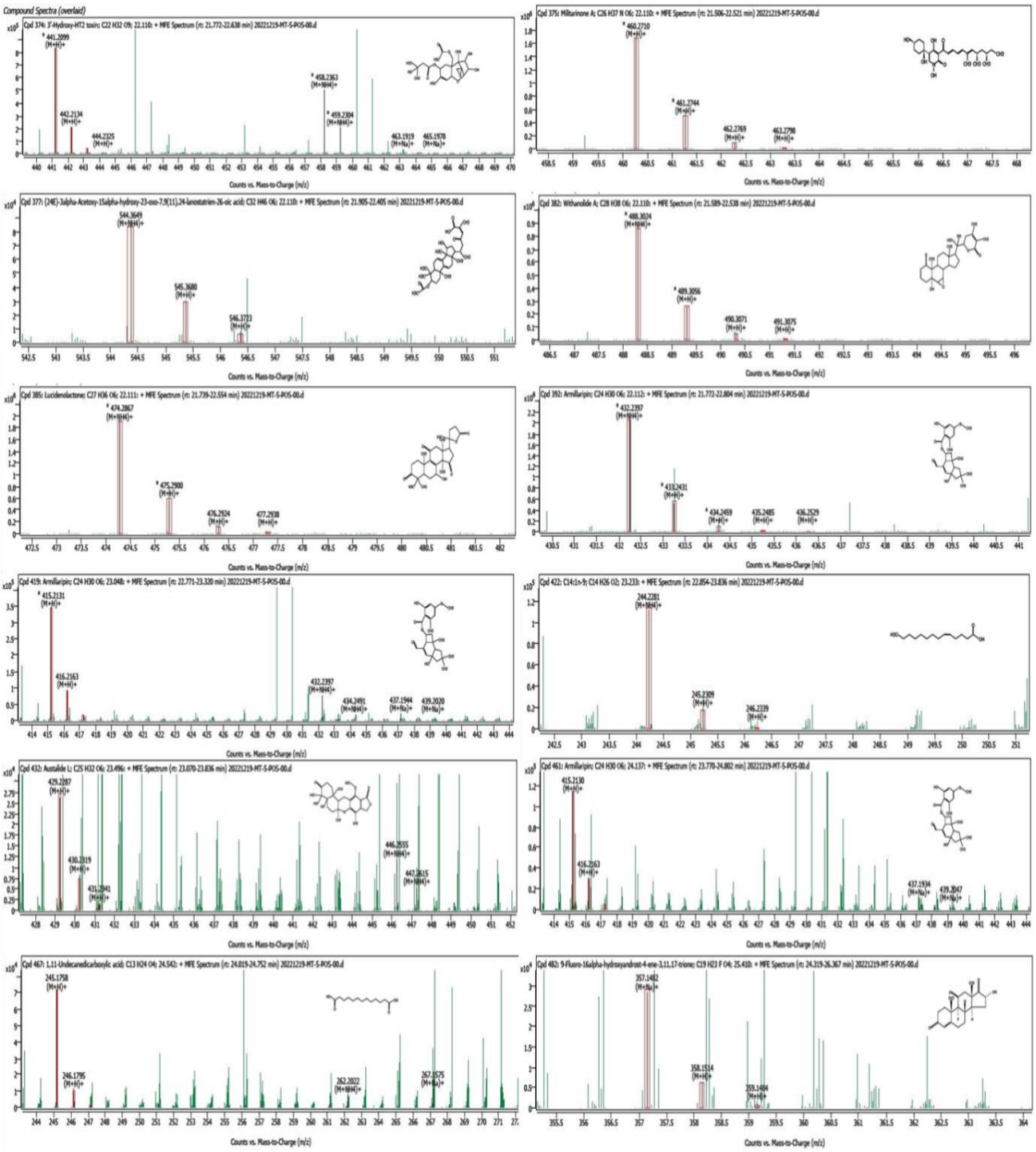

Figure 6: Compound spectra along with its structures of secondary metabolites detected by positive mode of LC-MS (Compound number 25- 36 from Table 2)

Figure 7 and 8 showed the compound chromatograms and spectra of compounds 37-48 (from Table 2) along with its structures, respectively.

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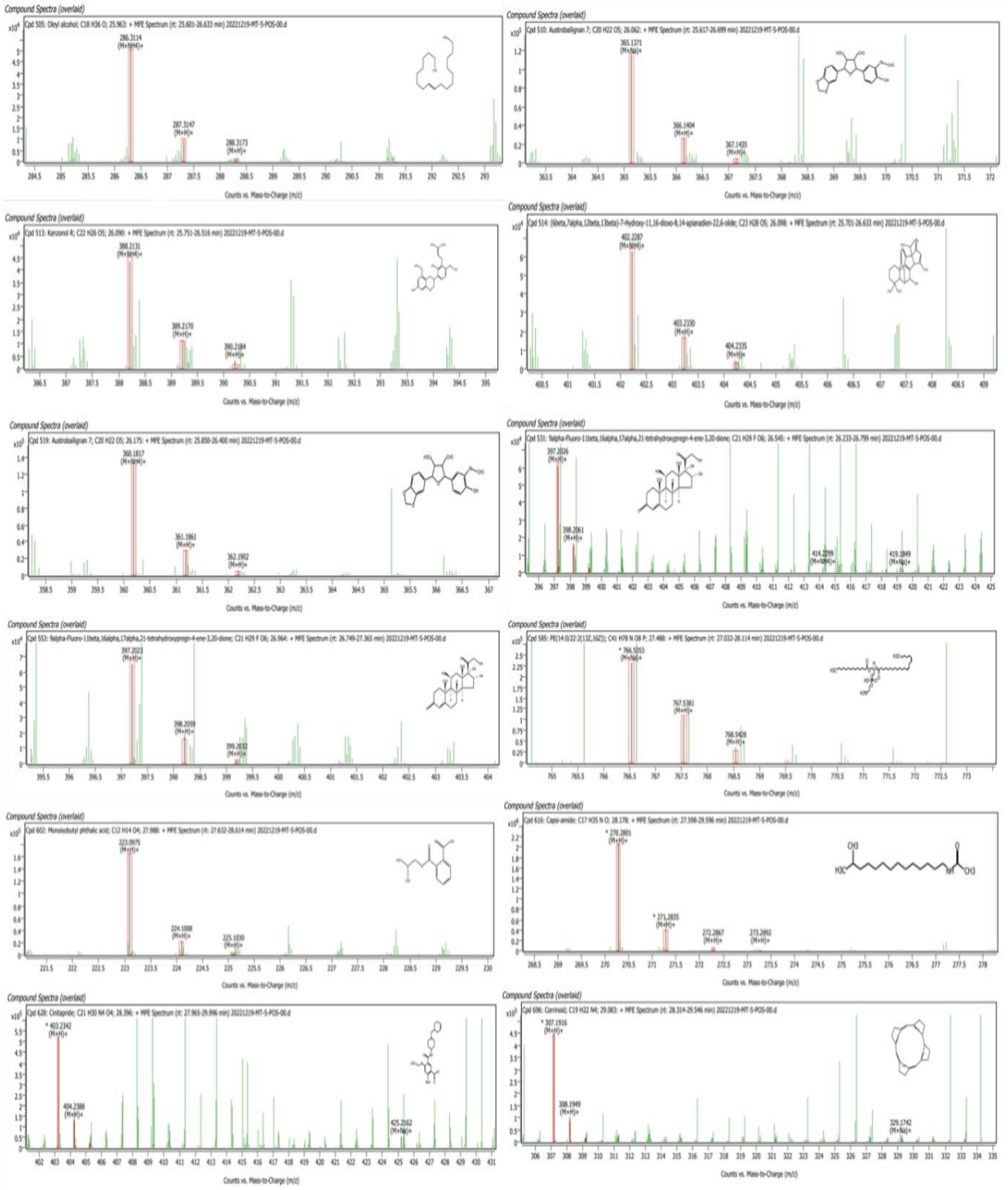

Figure 7: Compound chromatograms of secondary metabolites detected by positive mode of LC-MS (Compound number 37-48 from Table 2)

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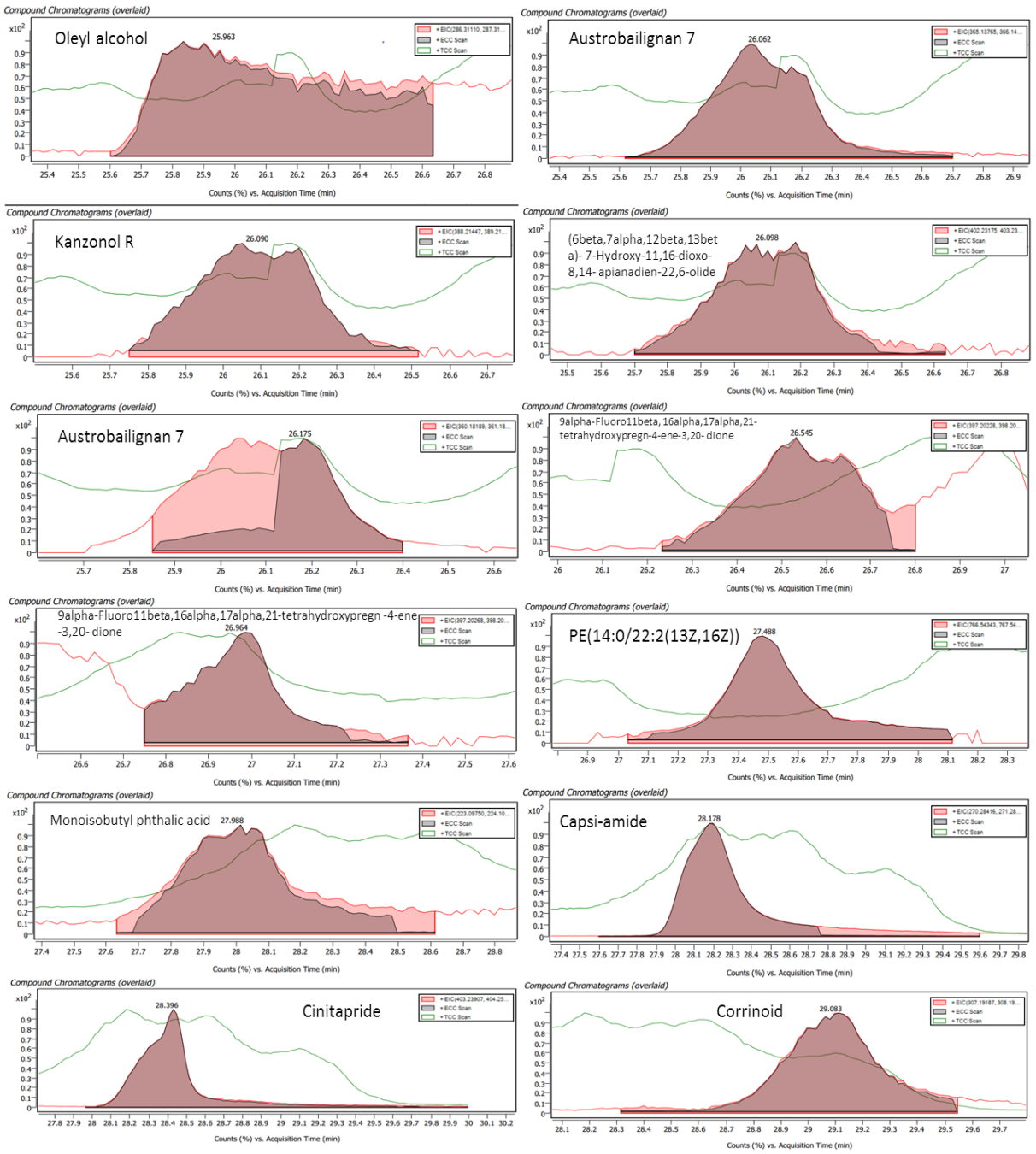

Figure 8: Compound chromatograms of secondary metabolites detected by positive mode of LC-MS (Compound number 37-48 from Table 2)

3.2 Compounds identified by negative mode of LC-MS

Total 17compounds were identified in the negative mode of the LC-MS. Four compounds are characterized. There structural formula, RT and mass are given in Table 3.

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Table 3: Compounds identified in negative mode of LC-MS

Sr. No.	Compound name	Structural formula	RT	Mass
1	3-b-Galactopyranosylglucose	C12 H22 O11	2.236	342.1172
2	trifluoroacetic acid	C2 H F3 O2	2.718	113.9930
3	Tetrahydropteridine	C6 H8 N4	16.722	136.0743
4	Lauryl hydrogen sulfate	C12 H26 O4 S	25.191	266.1559

Figure 3 and 4 showed the compound chromatograms and spectra along with its structures, respectively.

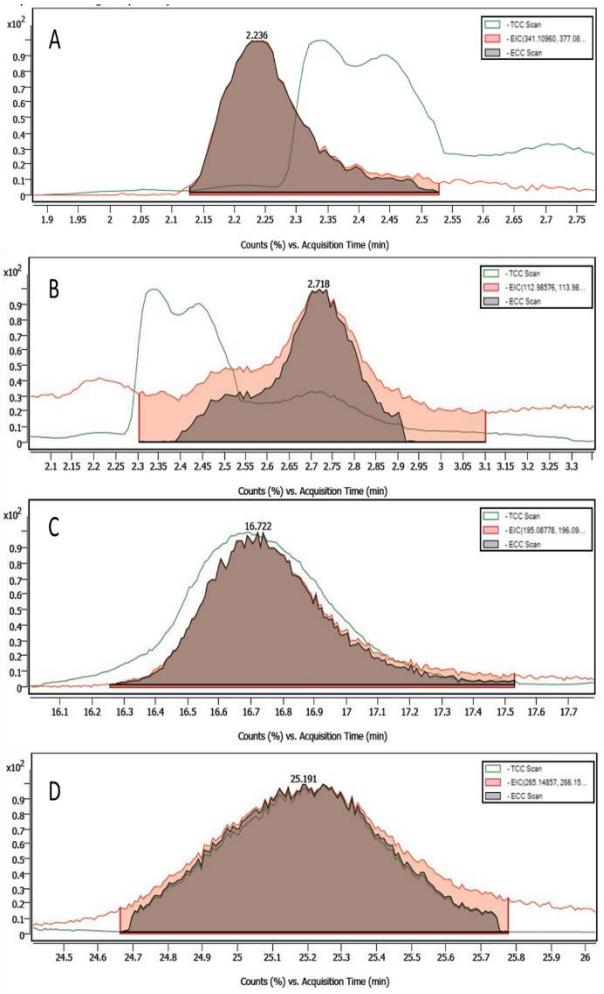

Figure 9: Secondary metabolites detected in the negative mode of LC-MS

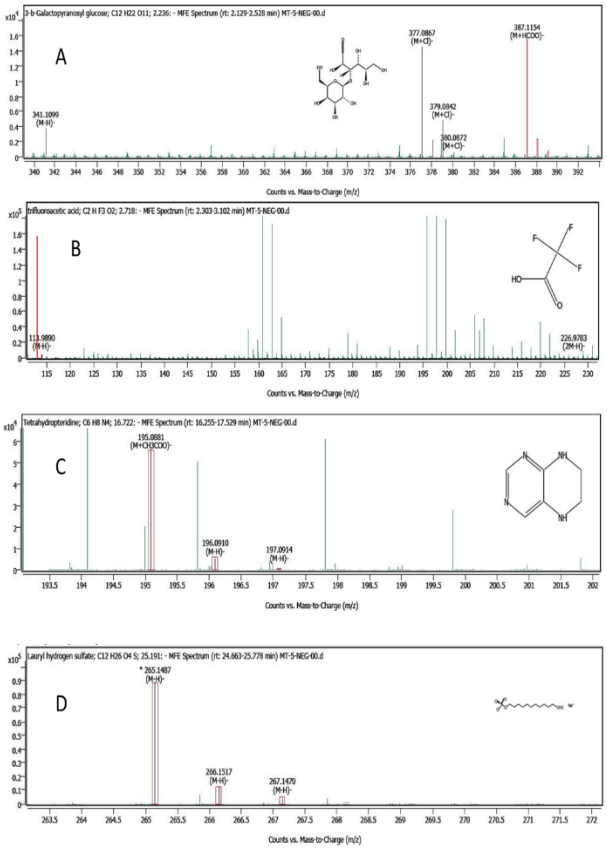

Figure 10: Compound spectra along with its structures of secondary metabolites detected by negative mode of LC-MS

4. Discussion

The *Scrophularia nodosa* plant was reported to have many health beneficiary and therapeutic compounds (4). Giner et al., (1998) reported scrovalentinoside was major iridoid found in the *Scrophularia lucida* L based on the MS and NMR studies. Many authors'published spectroscopic data on Scrophularia species i.e. *S. auriculata* L. ssp. *pseudoauriculata* (Senn.) (24); *S. nodosa* L. (26); Scrophularia buergeriana (Miquel) (29); Scrophularia scopolii [Hoppe ex] Pers. var. scopolii (30); etc. Bhandari et al.(1992) and Lewenhofer et al. (2018)

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reported koelzioside as a major iridoid from *Scrophularia koelzii* L. Similar report was published for *Scrophularia deserti* Del. (28). Our results are accordance with these reports.

The content assessment of the main active compounds in different powder fractions of *Hedera helix* (L.) and *Scrophularia nodosa* (L.) revealed that intermediate and fine powders contained the highest concentrations of the active components (31).The quantitative determination by HPLC of the major compounds in the methanolic extract discovered homoplantaginin (3%), scrovalentinoside (1.4%), and koelzioside (0.7%) (34). In the present study the *Scrophularia nodosa* showed number of active components.

Sesterhenn et al., (2007) reported many medicinal properties of *Scrophularia nodosa* (L.). The plant was used to treat ulcers and joint pains, wounds, and eczema. It also exhibits anti-inflammatory property(35,36,37). In folk medicine, this plant can be used against skin rashes as a laxative and diuretic agent. The principle secondary metabolites include polyphenols such as phenolic acids, and flavonoids and glycosides such asiridoid glycosides and harpagoside. In the present study also, many polyphenols were identified. Our results are accordance with this report.Among phenolic acids, caffeic acid has hypoglycemic properties and a strong antioxidant activity (37). Quercetin glycosides identified in this plant are quercetin-O-rhamnoside, quercetin-O-glucoside, and rutin, known for their antioxidant properties (38). The plant known to have antioxidative (40,41), anti-inflammatory, antibacterial, antiviral (42), anti-cancer properties (39,40) and neuroprotective therapeutic effects (36). Many secondary compounds identified in the present study reported to have the above mentioned therapeutic effects. So, it is important to evaluate the whole extract of *Scrophularia nodosa* against major diseases such as cancer.

5. Conclusion

In the present study, *Scrophularia nodosa* was evaluated for its secondary metabolite compositions. Total 48 and 17 compounds were identified in positive and negative mode of LC-MS. Many active compounds from *Scrophularia nodosa* are known to have therapeutic potentials. The plant is used as homoeopathic medicine for various disease condition. In future, the anticancer, antioxidant activity can be evaluated to check its biological activity.

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